P. K. BULATOV

MODERN METHODS OF TREATING BRONCHIAL ASTHMA

FOREIGN LANGUAGES PUBLISHING HOUSE

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INTRODUCTION

Bronchial asthma is a grave disease occurring quite frequently in internal-disease clinics. There does not exist as yet any radical method of treating this malady; nor is there any definite opinion as to its aetiology or pathogenesis. Hence therapeutists must perseveringly search for new methods of treating bronchial asthma.

According to A. Rodossky, S. P. Botkin, N. F. Golubov and other Russian scientists of the latter part of the 19th and the beginning of the 20th century, it is a reflex mechanism that underlies the origin and course of bronchial asthma. In the last decade, thanks to the achievements of the Pavlov physiological school, clinicians and physiologists (Y. P. Frolov, P. K. Bulatov and M. Y. Aryev) have evolved on the basis of the reflex theory the cortico-visceral conception of aetiology and pathogenesis of this disease. The new outlook, arising out of I. P. Pavlov's and S. P. Botkin's conception of nervism and the cortico-visceral theory, led us to revise our old methods of treating bronchial asthma and to introduce new methods: administration of anti-bacterial preparations—penicillin and sulfanilamide preparations, and Academician V. P. Filatov's method of treatment by means of grafting. It made us take a new stand with regard to treatment with novocaine, etc.

This paper is intended to acquaint the reader with the work performed at the hospital therapeutical clinic of the Pavlov Medical Institute in Leningrad.

CHAPTER I

AETIOLOGY AND PATHOGENESIS OF BRONCHIAL ASTHMA

A great variety of pharmaceutical, physiotherapeutic and other methods of treatment (vaccinotherapy, serotherapy, pyrotherapy, etc.) are at present suggested for the treatment of patients affected with bronchial asthma.

In most cases, however, there is no definite indication when these remedies have to be administered; whether it be in the period of remission, or, on the contrary, in the period of exacerbated attacks; whether the preparation should be administered at all when complications of the basic disease develop, such as chronic vesicular emphysema, cardiac or pulmonary insufficiency, etc. Nor have we found any recommendations as to the interdependence between the relative effectiveness of the preparations and the duration of the disease. It has been observed that very many preparations relieve patients who have suffered from bronchial asthma for only a few months and that these preparations do not produce the desired effect in cases of ten-twenty years duration.

In describing the treatment of bronchial asthma, handbooks and journal articles most frequently recommend therapeutical measures of a symptomatic character.

We regard bronchial asthma from the viewpoint of I. P. Pavlov's and S. P. Botkin's ideas of nervism. It is a reflex mechanism that underlies the development of the disease. All the three links of this mechanism account for the development of the pathological process: 1) stimulant, which

acts on the nerve centres through the centripetal nerves and their endings; 2) the nerve centres which transmit the stimulation on to the centrifugal nerves; 3) peripheral tissues with the centrifugal nerve endings disseminated within them.

Hence, we hold that symptomatic therapy should come second, and that the application of therapy should aim first and foremost at treating the body as a whole by acting on the central nervous system through its reflex mechanisms.

From the viewpoint of modern physiology, the organism of man as well as of animals should be studied in close interrelation with environment: the activities of the individual organs of the body and its reactions to external influences are definitely related to the activity of the cerebral cortex. All the functions of the internal organs are performed with the participation of the cerebral cortex: the latter influences the internal organs, and vice versa.

According to S. P. Botkin's neurogenic, i.e., reflex theory of internal diseases, pathogenetic agents, when reacting on the body and the tissues, produce a stimulation of the corresponding nerve apparatus within them, which transmits it to the nerve centres. It is the latter that determine the development of different symptoms of bronchial asthma including asthmatic attacks.

We consider bronchial asthma to be an allergo-infectious disease.

Infection localized in the respiratory tract—in the bronchi and the lungs—plays a big role in the aetiology and pathogenesis of bronchial asthma. Observations made on 1,200 patients showed that, in 98 per cent of the cases, infection of the respiratory tract preceded the first attack of bronchial asthma.

A considerable percentage of this infection was due to virus influenza and its complications, measles and whooping cough bronchites and pneumonias, chronic tonsillites, inflammations of nasal sinuses and other diseases of the respiratory organs. In the case of 2 per cent of the patients

the causes of the first attack of asthma have not been discovered.

The above observations confirm the data previously published: S. M. Genkin and M. V. Ovchinsky (1928) attributed the first attack of bronchial asthma to infection of the respiratory tract in almost 100 per cent of their patients; S. G. Gotesfried and E. Y. Heinrichsdorf (1941)—in 66 per cent; N. N. Malkova (1936)—in 75 per cent; Moncorgé—in 100 per cent, and Grimm—in 64 per cent of their patients.

What, then, accounts for the aetiopathogenesis of bronchial asthma? Our data suggest that infection of the respiratory tract is the principal cause which brings about the change in its mucous membrane. Our concept is confirmed by a postmortem histological examination of the respiratory tract mucosa of 14 patients affected with bronchial asthma. Cylindrical epithelium, for example, after being affected with virus bronchites and bronchopneumonias, dies away, laminates into layers and is replaced by multilayer flat epithelium, which leads to an alteration in the normal protective function of the mucous membrane of the bronchi and respiratory tract.

Thus, conditions are created whereby substances generally harmless for the body become toxic. V. F. Undrits believes that infections remove the protective barrier of the mucous membrane; in addition, during acute or exacerbated chronic infections, the products of bacteria disintegration, toxins and substances resulting from the disintegration of the bronchus tissue, are sucked into the blood through the mucous membrane of the bronchi, and sensitize the organism.

Sensitization means a change in the normal sensitiveness of the organism towards an increase. The penetration of toxins and of disintegration products of the lung and bronchus tissues appears to lead to a stimulation of the bronchus receptor apparatus. The constant stimulation of the receptor apparatus of the bronchi and lungs is also transmitted to the central nervous system.

Given a specific condition of the stimulation and the

nervous system, a sufficiently stable, though weak, excitation of the nerve centres becomes a dominating factor in the activities of the nerve centres—the nuclei of the vagus, the thalamus opticus and the cortex. The doctrine of the dominant is a doctrine on the temporary domination of a focus of excitation or heightened excitability which appears in one or another part of the central nervous system under the influence of stimulations. The latter are characterized by a definite frequency and intensity and act on the nerve centres by way of reflex—through the centripetal fibres or directly through the blood.

"Constantly performed work or the working posture of the body," A. A. Ukhtomsky wrote, "is the outer expression of the dominant."

In its turn, the focus of heightened excitability (the pathological dominant of bronchial asthma), formed in the central nervous system under the influence of impulses which arise in the nerve endings of the respiratory tract, affects the parasympathetic part of the nervous system, causing a spasm of the bronchi and changing the secretory function of their mucous glands.

As a result, we see clinically the development of an attack of bronchial asthma. A study of the properties of the dominant helps in explaining the pathogenesis of bronchial asthma.

Having arisen, the dominant is firmly preserved in the nerve centres and is sustained by various outside stimulations. The attacks of bronchial asthma, once they have appeared, may subsequently be brought about by various causes: odours, meteorological conditions, positive, negative emotions and other causes. The greater the number of nerve elements participating in the formation of the dominant, the longer its effect.

It is this property of the dominant—inertia—which explains the fact that bronchial asthma, once it has appeared, follows its course, though the initial excitation stimulus is no longer there.

The dominant is capable of deflecting from their normal course excitations flowing into the neighbouring nerve centres; it is capable of attracting them and of being maintained at their expense.

This character (the capacity for the summation of excitations) makes it possible to explain the way in which different causes (primarily diseases of the respiratory organs and external factors) may aggravate the course of the disease and bring about more frequent attacks. The dominant does not completely disappear even after subsiding. It may subsequently reappear under the influence of various causes. This property of the dominant (its restoration) accounts for the recurrence of bronchial asthma attacks after a long period of seeming recovery. The dominant ceases to exist (fades away) either because the stimulation that originated it has stopped functioning, or because a new and stronger dominant has come into existence. Thus, the emergence of a rival emotional dominant may result in the termination of the asthmatic state or bronchial asthma attacks.

Hence, from the viewpoint of Russian physiological science, a number of points can be explained which are of great significance in the aetiology and pathogenesis of bronchial asthma. A lasting infection of the respiratory organs of patients suffering from bronchial asthma is the focus from which impulses are transmitted to the central nervous system, thereby creating in the latter dominant foci of heightened excitability—the corresponding pathological dominant of bronchial asthma.

A disease, caused by the presence of a pathological dominant (as conceived by A. A. Ukhtomsky) or of "stagnant excitation" (according to I. P. Pavlov), calls for treatment, primarily directed at the central mechanisms.

It follows from the above that, when treating bronchial asthma, it is necessary first of all to protect the central nervous system from impulses which arise in the toxic infectious foci, located in the bronchi, lungs and other parts

of the respiratory tract. Nor should we overlook pharmacological treatment, aimed at abating inflammatory phenomena along the respiratory tract which helps in reducing the sensitization of the body.

In our view, infection of the respiratory tract accounts for the stimulation of the interoceptors, terminating in the mucous membrane of the trachea and bronchi, which creates the prerequisites for the emergence of centripetal impulses; the latter penetrate into the nuclei of the vagus and the thalamus opticus, and into the cerebral cortex, producing there dominant foci of heightened excitability. The pathological dominant thus created sustains the heightened tone of bronchial muscles and leads to their subsequent hypertrophy; it also intensifies the secretory function of the mucous membrane glands of the bronchi, which in its turn leads to the disturbance of the respiratory function of the lungs, followed by the development of emphysema of the lungs.

When changes in the mucous membrane take place, the products of disintegration of the tissues and bacteria pass into the blood stream and sensitize the organism.

In examining the problem of treating bronchial asthma, we analyze below each method of treatment individually: anti-bacterial and protective therapy of the central nervous system, psychotherapy, and other kinds of therapy. The last chapter deals with first-aid methods in cases of bronchial asthma attacks.

CHAPTER II

TREATMENT OF BRONCHIAL ASTHMA

1. ANTI-BACTERIAL THERAPY

The high therapeutic activity of sulfanilamides and penicillin was the reason for using them to cure patients suffering from bronchial asthma and receiving treatment in our clinic at the First Medical Institute in Leningrad. This was justified by the presence of acute or chronic infection of the respiratory organs, which preceded the bronchial asthma disease in 98 per cent of cases, as well as by the fact that in the course of the disease in 96 per cent of patients the infectious-toxic factor was the chief cause bringing about recurrent attacks of bronchial asthma.

The number of patients affected with bronchial asthma and treated with sulfanilamides and penicillin totalled 350; of these 205 were in-patients and 145 out-patients. The observations covered a period of from six months to ten years.

First group (172 patients). The patients received only sulfanilamides according to the following schedule: first day—6 gm., second day—5 gm., and the days following—4 gm. a day. In the course of treatment from 30 to 60 gm. were administered. White streptocide was administered to 22 patients, sulfidin—to 26, sulfazole—to 49, sulfathiazole—to 22, disulfan—to 30, and other sulfanilamides—to 23 people.

Second group (52 patients). The patients received intramuscular penicillin injections every four hours. From 40,000 to 100,000 I.U. of penicillin were injected into the

outer upper quadrant of the gluteal region. The patient received from 200,000 to 600,000 I.U. of penicillin a day. In the course of treatment, from 2,500,000 to 21,500,000 I.U. of penicillin were administered.

Third group (22 patients). The patients received intravenous injections of penicillin. From 100,000 to 300,000 I.U. of penicillin were administered into the cubital vein twice a day. Every patient received from 200,000 to 600,000 I.U. of penicillin a day.

Fourth group (16 patients). Every patient was given simultaneously an intravenous injection of from 100,000 to 400,000 I.U. and an intramuscular injection of from 300,000 to 400,000 I.U. of penicillin daily.

Fifth group (88 patients). Of these 66 patients were treated alternately with sulfanilamides and penicillin, while 22 received simultaneously sulfanilamides and penicillin according to the above dosage.

I. At first the patients of the first group were treated with white streptocide. Eleven patients had an acute infection and eleven suffered from complications. Streptocide exercises a bacteriostatic influence on the gram-positive group of microbes. The application of white streptocide in cases of exacerbated infection of the respiratory tract was always effective, although, when using other sulfanilamides, the therapeutical results were more pronounced. The asthmatic condition of patients affected with infectious foci in the lungs improved at the end of the first or the beginning of the second day after the administration of 5-8 gm. of sulfanilamide preparations, sulfazole or sulfathiazole. The patients were able to sleep without being compelled to remain in a sitting posture, and to exhale more freely. With the treatment continued, we observed a lowering of temperature, an abatement of local inflammatory phenomena in the bronchi and lungs (less crepitation and sputum). Roentgenoscopy showed a diminution of stagnant phenomena in the lungs. Leucocytosis was reduced and the differential blood count and the E.S.R. returned to normal.

After the termination of the course of treatment, the asthmatic state or attacks did not recur in 48 cases, while in 35 instances a relapse was observed. In the case of patients suffering from complications (vesicular emphysema of the lungs, chronic non-specific pneumonias, etc.) the results of treatment were less pronounced: in 33 cases the attacks ceased during our observations, and in 48 cases they continued, though in a less marked way.

In two cases, where no infection foci were present, the attacks were stopped for a protracted period (up to a year). In six other cases the attacks continued, though in a less pronounced form.

In the case of 32 patients affected with chronic non-specific pneumonia, when prophylactic treatment with 1 gm. of sulfanilamide two or three times a day was recommended, attacks of bronchial asthma, which generally set in after the inhalation of various odours (smoke and dust, moist or cold air, etc.) were prevented for a period of two-three months.

The effect was most pronounced when our patients were treated with sulfazole and sulfathiazole, and less marked when treated with white streptocide.

The table below summarizes the therapeutical effect of sulfanilamide preparations on our patients.

Table 1

	Infection foci	No infection foci present	Complications	Total number
Number of patients	83	8	81	172
Results of treatment: improvements .	48	6	33	87
Results of treatment: no change . . .	35	2	48	85

We believe that the positive effect obtained in patients suffering from complicated bronchial asthma and affected with infection foci was due to the bacteriostatic and, pos-

sibly, to the bacteriolytic action of the sulfanilamides. When the bacteria and their toxins disappear from the respiratory organs, the interoceptors of the respiratory tract no longer receive stimulations. The impulses directed along the centripetal nerves into the central nervous system stop, and the attacks cease. This reasoning of ours is confirmed by the fact that when the infection was sulfanilamide-resistant the attacks did not cease.

It is more difficult to explain the positive effect obtained in patients without infection foci when prophylactic treatment with sulfanilamides is applied.

A comparison of the action of sulfanilamides with that of other preparations previously prescribed for patients affected with bronchial asthma both as a medicine and prophylactic (pyramidon and aspirin) shows that they act in approximately the same way.

By administering sulfanilamides, we prevented attacks of bronchial asthma and in some cases checked the asthmatic state. Hence, it may be assumed that sulfanilamides act on the central nervous system, i.e., on the cerebral cortex, in the same way as pyramidon and aspirin, and have desensitizing effect as well. This property of sulfanilamides is little known as yet.

Our observations have been confirmed by data published in Soviet medical literature. Thus, in studying the effect obtained from administering sulfanilamides, N. V. Lazarev and L. S. Salyamon distinguish two factors: the antibacterial and anti-inflammatory ones. In his experiments on rabbits M. L. Gershanovich found that hypothermy arising from a subcutaneous injection of tetrahydrobetanaphthylamine abates if the animal is simultaneously administered internally sulfidin or sulfathiazole.

M. D. Moshkovsky's experiments on rabbits show that sulfanilamide preparations drastically reduce the reaction of the body to the intracutaneous introduction of the intestinal group bacteria vaccines.

Hence, judging by our own findings and data available

in various publications, sulfanilamides exercise a desensitizing and not only a bacteriostatic influence.

This property, as shown by our observations, can be utilized in the treatment of bronchial asthma. Sulfanilamides may also be applied prophylactically in cases when it is definitely known that the patient will be exposed to the effects of harmful factors, or when the patient is taken seriously ill or suffers from an exacerbation of a chronic disease of the respiratory tract, which cause bronchial asthma attacks.

II. We have been using penicillin for the treatment of bronchial asthma patients since 1945. Penicillin has been applied in cases of bronchial asthma with the aim of reacting on the gram-positive group of bacteria which sustains the infection of the respiratory tract and lungs.

As a result of the application of penicillin in cases of infection of the respiratory tract the bacteria and toxins of the gram-positive group disappear from the respiratory organs. The interoceptors of the respiratory tract stop receiving stimulations and directing them along the centripetal ways into the central nervous system, following which the attacks and asthmatic state cease, and to all intents and purposes the patient recovers. When the infection was penicillin-resistant the attacks continued with unabated frequency and force.

We applied intramuscular injections of penicillin with marked success, and in 1948 went over to intravenous injections. This was necessitated by the need of creating great concentrations of penicillin in the respiratory tract. When introduced into venous blood, penicillin passed into the lungs and directly to the infection focus.

It may be presumed that, when passing through the capillary network of the lungs, penicillin is fixed by the tissue of the lungs, which results in its higher concentration.

A group of 52 patients treated with intramuscular injections of penicillin included 22 with acute infections of

the respiratory organs, 2 without any infection in the respiratory organs, and 28 suffering from complications (chronic vesicular emphysema of the lungs, chronic non-specific pneumonia, etc.).

Eighteen patients suffering from an acute infection of the respiratory tract, when treated with penicillin, showed an improved general condition and better appetite on the second or third day of treatment. The attacks and the asthmatic state ceased on the third or fourth day. In the course of treatment, particularly in cases of patients receiving no less than 500,000 I.U. of penicillin a day, the leucocytosis and the shift of the differential blood count to the left declined, and the sedimentation rate dropped.

By the end of the course of treatment the number of leucocytes reverted to the average norm, the differential blood count assumed its norm, the E.S.R. fluctuated within a range of 6-12 mm. per hour, and the temperature became normal. A long remission set in, lasting from six months to two years.

In the case of the four remaining patients of this group, the attacks likewise disappeared on the third or fourth day. They reappeared, however, on the 6th-9th day of treatment and subsequently their course was the same as before treatment. There were no changes in the leucocytosis, in the shift to the left of the differential blood count or in the sedimentation rate. The impression one gained was that penicillin did not influence the infection to any marked degree.

In the case of two patients without any infection penicillin treatment proved futile. The general improvement which set in was of short duration. The number of leucocytes, the differential blood count and the E.S.R. of the patients remained unchanged.

The general condition of ten patients suffering from complications improved on the second or third day of treatment with penicillin. The attacks became less pronounced, the number of leucocytes decreased, the differential blood

count became normal, and the sedimentation rate dropped. A remission set in.

The other 18 patients showed no marked improvement, and the attacks continued.

In another group (22 patients) penicillin was introduced intravenously. In the case of eight patients of this group with an acute infection of the respiratory organs penicillin already exerted its influence by the end of the first day. The temperature dropped to normal or even to subnormal and the general condition improved. The patients were able to sleep in a lying posture. A roentgenological examination showed an abatement of stagnant phenomena in the lungs. The sedimentation rate was for some time still above normal. The number of leucocytes and the ratio of cells in the differential blood count became normal. There was no longer any need for injecting adrenaline.

A comparison of the action of equal dosages of intramuscular and intravenous penicillin injections shows that the latter appear to possess all the advantages.

Case No. 137-759 will serve as illustration.

Patient B. B., female, aged 46, admitted to the hospital clinic on December 2, 1947. Suffered from bronchial asthma since the age of 42. Attacks set in after chills and colds. The patient's mother had been ill with chronic asthmatic bronchitis. The patient entered the hospital in a severe asthmatic state with residual phenomena of bronchopneumonia. B. was given five or six injections of adrenaline (1:1000) a day. After the injection dyspnea disappeared for an hour or two. The temperature was subfebrile, the leucocytosis—14,800, and the sedimentation rate—18 mm. per hour. The patient received penicillin intravenously in doses of 200,000 I. U. twice a day. All in all 4,000,000 I. U. were administered. On the second day the temperature dropped to normal. In six days the number of leucocytes decreased to normal, and in eight days the E.S.R. became normal. On December 29, the patient was discharged in a good condition. No attacks ensued for a period of nine months.

No penicillin was injected intravenously in cases without infection foci in the lungs. According to our observations, out of twelve patients suffering from complications and receiving both intramuscular and intravenous penicillin

injections, eight showed a marked improvement as compared with patients who received only intramuscular penicillin treatment.

The favourable therapeutical results we had obtained when applying intravenous injection of penicillin warranted the combined use of penicillin: 18 patients affected with bronchial asthma received intravenous injections of from 100,000 to 400,000 I.U. of penicillin a day, and intramuscular injections of from 200,000 to 600,000 I.U. We observed good results in six patients suffering from an acute infection and in eight patients suffering from complications.

The general state improved after the first few days of treatment. The asthmatic state disappeared, and the patients were able to sleep in a lying posture. After the course of treatment a remission set in lasting three months or more.

Case No. 282-761 is cited below.

Patient B., aged 40, was admitted to the clinic on January 6, 1949, in a grave condition lasting over three weeks. The patient had suffered from bronchial asthma since the age of five. The patient's grandfather on the father's side and his father were affected with bronchial asthma. B. suffered from attacks of asthma after exposure to cold and, as a rule, after acute rhinitis or aggravations of bronchitis.

In the clinic the asthmatic condition of the patient continued for over ten days. He received from five to seven injections of adrenaline a day.

The injections were followed by an improvement lasting one or two hours, and then asphyxia set in again. A course of treatment with penicillin was begun: intravenous injections of 100,000 I. U. and intramuscular injections of 200,000 I. U. a day. All told, 4,500,000 I. U. were administered. Two days later the general condition improved, and the attacks stopped. The remission lasted a year.

III. No effect was produced in 88 patients treated with sulfanilamides or penicillin. The infections of the respiratory tract proved to be resistant to sulfanilamides and penicillin, and it was therefore thought advisable to apply combined penicillin and sulfanilamide therapy. It turned out that in cases when sulfanilamides or penicillin proved

of no avail, the combined treatment produced a marked effect.

Sulfanilamides were administered according to a definite schedule. From 400,000 to 500,000 I.U. of penicillin were introduced intramuscularly every day, the patients receiving all in all an average of 6,000,000 I.U. throughout the course of treatment.

In 28 cases of acute infection good results were obtained: the E.S.R. and the number of leucocytes became normal, and the shift to the left disappeared.

Favourable results were also obtained in the case of 38 patients suffering from complications. In 18 patients the effect was not distinct, and the attacks continued.

Finally, no marked curative effect was obtained in four patients who did not suffer from infection of the respiratory tract.

To confirm our findings of the action of penicillin and sulfanilamides on bacteria, we examined the bacterial flora of the sputum of 51 patients before and after treatment.

These examinations were made at the bacteriological laboratory of the Pavlov Medical Institute in Leningrad.

Before treatment, the following prevailed in the sputum: in 22 cases—haemolytic streptococcus, in 17 cases—Streptococcus viridans, and in 7 cases—pneumococcus.

In addition, other micro-organisms were isolated from the sputum: staphylococci, catarrhal micrococci, gram-negative bacilli, sarcinae, etc.

Relevant publications on the subject state the following: M. I. Shtutser found in the sputum of 18 patients 36 species of micro-organisms: first came streptococci and pneumococci followed by staphylococci, Friedlender's pneumococci and the pseudo-diphtherial bacillus. Wiemer and Cobe compared the qualitative and quantitative composition of microflora of patients' sputum with that of the sputum of 200 healthy people. The percentage of micro-organisms in the sputum of patients affected with bronchial asthma and of healthy people proved to be as follows: the percentage

of staphylococci in healthy people was 54, in patients—28.6; the respective figures for catarrhal micrococci were 63.6 and 34.5, for pneumococci 54.5 and 64.2, for streptococci 46 and 67.4, and for sarcinae 23 and nil.

Goeb found haemolytic streptococcus in the sputum of 80 per cent of children affected with bronchial asthma.

Kemmerer often discovered Streptococcus viridans in the sputum of patients suffering from bronchial asthma.

Hence, going by our own data as well as the data of various publications, streptococci are most prominent in the sputum of patients affected with bronchial asthma, then come pneumococci and other micro-organisms.

It is worth noting that streptococci and pneumococci, according to N. D. Strazhesko's observations, play a considerable role in the sensibilization of the body.

In the case of our patients streptococci and pneumococci disappeared from the sputum after a course of treatment with penicillin and sulfanilamides, but other species of micro-organisms appeared in their stead, notably bacteria of the intestinal bacillus type.

According to Southwell, Humphrey, Joules and others, gram-positive micro-organisms disappeared and gram-negative micro-organisms increased in the sputum of bronchial asthma patients after treatment with inhalations of penicillin.

We attribute the phenomena to the discontinuance of the antagonistic action of the gram-positive group of bacteria. The arresting action of the latter on the growth of gram-negative bacteria was observed by some experimenters in clinics and laboratories. We, too, found confirmation of these data in patients treated with penicillin.

When using penicillin for the treatment of patients suffering from bronchial asthma and an acute infection, we first of all eliminate the toxic-infectious factor, while the allergic phenomena remain. When penicillin and sulfanilamides are administered simultaneously, the therapeutical effect is in-

creased, apparently due to the desensitizing action of the latter.

When applying penicillin and sulfanilamides for the treatment of patients, particularly in the first stage of bronchial asthma, we may expect to retain or restore the normal barrier function of the mucous membrane of the respiratory tract and thereby prevent any further allergization of the body.

It was far more difficult to treat patients suffering from bronchial asthma complicated by chronic vesicular emphysema of the lungs, non-specific chronic pneumonia, etc., when penicillin and sulfanilamide therapy failed to produce the desired results and combined treatment proved satisfactory because of the desensitizing and anti-bacterial influence on the gram-negative and gram-positive flora. These patients suffered from chronic infection and altered reactivity of the mucous membrane of the respiratory tract, with complications in the form of emphysema of the lungs. Therefore, positive results in the treatment of such patients were recorded in half as many instances as was the case with patients suffering from an acute infection of the respiratory tract. Hence, the combined treatment with sulfanilamides and penicillin is, as shown below, one of effective methods of treating bronchial asthma patients. Sulfanilamides and penicillin change the bacterial flora of the respiratory tract, thereby removing the stimulation of the interoceptors of the bronchi and the central nervous system, with a resulting fading of the dominant.

As might have been expected, patients suffering from bronchial asthma but manifesting no infection in the bronchi or lungs showed no improvement when treated with penicillin.

We also applied other kinds of therapy of which adrenaline, ephedrin and caffeine deserve particular attention. We prescribed ephedrin internally three times a day in doses of 0.03-0.05 gm. In severe cases, particularly when dealing with patients suffering from complications, we prescribed

1.0 gm. of adrenaline once or twice a day subcutaneously. Pure caffeine was administered internally in doses of 0.03-0.05 gm. and caffeine sodio-benzoate in doses of 0.05-0.1 gm. three times a day. Patients suffering from complications received ephedrin and caffeine simultaneously in the aforementioned doses. The patients were prescribed these preparations as a course of treatment. Our aim in prescribing caffeine was to intensify the coronary blood circulation, to increase the efficiency of the myocardium and at the same time to exert a direct stimulating influence on the vasomotor centre.

The administration of these preparations to patients in the period of treatment with penicillin and sulfanilamides is fully justified, since in most cases the little effectiveness of the therapy practised on patients depends on the disfunction of the sympathetic part of the vegetative nervous system as a result of the suppression of the higher nervous system in patients affected with bronchial asthma during attacks.

We recorded many instances of patients of 40 and upwards, affected with an acute or chronic infection of the lungs, having cardiac insufficiency of the first and sometimes the second degree during and after attacks or a protracted asthmatic state. In such cases we prescribed caffeine, theobromine, diuretin, lychnis—or digitalis in dosages usually applied when treating patients suffering from cardiac insufficiency.

When polyhypovitaminosis appeared, we recommended polyvitamin therapy. The application of this complex therapy did not bring about a complete recovery of patients suffering from bronchial asthma. Our immediate task was to eliminate the infection of the respiratory tract so as to stop all further allergization of the body, to desensitize it and thus check attacks of bronchial asthma and the asthmatic state.

In the case of 75 per cent of the patients, when penicillin and sulfanilamides were used for treatment, the attacks

and asthmatic state ceased for a period lasting from three months to three years. The patients recovered and resumed their occupations.

During a remission particular attention should be paid to prophylactic treatment and the elimination of the external factors which bring about an exacerbation of the infection of the respiratory tract and lead to a disturbance of the function of the central and vegetative nervous systems.

The following conclusions may be drawn from the above:

1. Treatment of patients suffering from bronchial asthma with penicillin and sulfanilamides is indicated in the period of acute and chronic infections of the respiratory tract.

2. Penicillin should be administered in doses of 500,000 I.U. a day and 5,000,000 I.U. throughout the course of treatment, and sulfanilamides in doses of 30 to 40 gm. for the course of treatment.

3. Treatment with intravenous penicillin injections of patients suffering from bronchial asthma with attending infection of the lungs and bronchi is recommended, but combined treatment with intramuscular penicillin injections is more effective. Combined treatment appears to create higher concentrations of penicillin in the lungs and the results are manifest within the first 24 hours.

4. Treatment with penicillin and sulfanilamides is contraindicated in patients who do not suffer from an infection of the respiratory tract.

5. Patients affected with bronchial asthma should be treated with penicillin and sulfanilamides in combination with drugs that act on the central nervous system, the sympathetic part of the vegetative nervous system and the cardio-vascular system.

6. Apart from their bacteriostatic action sulfanilamides also have a certain desensitizing effect in the treatment of patients.

7. In treating bronchial asthma patients with penicillin and sulfanilamides it is important to change the bacterial flora of the respiratory tract, and particularly to eliminate

streptococci, staphylococci and pneumococci, which exercise a stimulating influence on the receptors of the respiratory tract and sustain the dynamics of the disease and the sensitization of the body as a whole.

We used streptomycin as a cure in cases when the bacterial flora of the respiratory organs proved resistant when acted upon by sulfanilamides and penicillin.

All in all we had under observation 27 patients affected with bronchial asthma. They received subcutaneously from 500,000 to 1,000,000 I.U. of streptomycin a day. During the course of treatment the patients were given from 8,000,000 to 40,000,000 I.U. of streptomycin. After the course of treatment with streptomycin 16 patients were relieved of attacks for a period ranging from three to twelve months. In six cases the remission lasted over a year, and in five the bronchial asthma attacks continued, but with less intensity and frequency. This group consisted of patients affected with chronic vesicular emphysema of the lungs and myofibrosis of the heart combined with phenomena of pulmonary and cardiac insufficiency of the first or second degree.

Here is case No. 521.

Patient V. P., aged 28. Entered for dispensary treatment at the hospital therapeutical clinic on November 27, 1945 with complaints of frequent and lasting attacks of asphyxia.

P. had been suffering from bronchial asthma for over five months. The first attack took place a few days after broncho-pneumonia; before that he had suffered for several months from bronchitis. P. had been susceptible to colds since childhood and often suffered from catarrh of the upper part of the tract.

From 1945 to 1949 P. received dispensary treatment. In 1949, a routine bronchographic examination revealed tuberculosis of a bronchus, and tuberculosis bacilli in the sputum. The patient was placed in a lung clinic where he was treated with streptomycin. After the introduction of 2,000,000 I. U. of streptomycin all attacks ceased, and the general condition improved. No attacks were recorded in the period of treatment. The remission lasted over six months.

In the given instance streptomycin removed the intoxication coming from the tuberculosis focus located in the wall of the bronchus. The central nervous system was no longer

subjected to constant and lasting stimulations from the peripheral interoceptors of the bronchi. With the reflex arc between the lungs and the central nervous system interrupted, the attacks of bronchial asthma in the patient stopped. Thus the action of streptomycin was tested on patients suffering from tuberculosis of the lungs or the bronchus and on patients with sulfanilamide- and penicillin-resistant bacterial flora of the respiratory tract. A remission set in in cases when the action of streptomycin was effective. We consider that treatment with streptomycin of patients suffering from bronchial asthma should be recommended in cases when tuberculosis of the lungs or bronchus is manifest and when the bacterial flora of the respiratory tract is penicillin- and sulfanilamide-resistant.

We administered para-aminosalicylic acid to 24 patients affected with bronchial asthma. The patients received daily from 8 to 14 gm. of para-aminosalicylic acid and a total of 300 to 600 gm. for the whole course of treatment. The indications for prescribing this preparation to patients affected with bronchial asthma were more or less the same as for streptomycin.

According to N. V. Vershinin, the absorption of oxygen by tuberculosis bacilli is impeded, simultaneously the process of oxidation within them is retarded and their growth and vitality is depressed. In the course of treatment the general condition of all 24 patients improved. The bronchial asthma attacks became of shorter duration and less pronounced, and their number decreased. In 8 cases a prolonged remission lasting from six to eight months was recorded. Our observations show that para-aminosalicylic acid also affects other groups of micro-organisms; it should also be noted that to some extent it exercises a desensitizing effect on the body of patients suffering from bronchial asthma.

We began to treat bronchial asthma patients with phytoncides of garlic in 1952. Solutions of garlic juice, dissolved in proportions of 1:5 and 1:10, were injected intratracheally

in doses of 10, 15 and 20 ml. The technique of introducing phytoncide solutions is analogous to that applied in bronchography. In the course of treatment from 5 to 10 intratracheal injections were made to patients suffering from bronchial asthma and chronic infection of the bronchi and lungs. Good results were obtained in each of the five cases.

It should be noted that at the beginning of the treatment an exacerbation was recorded followed by a remission lasting from 3 to 15 months.

Our observations lead to the conclusion that a lasting infection of the respiratory organs of bronchial asthma patients is the site from which the impulses are transmitted to the central nervous system, bringing it into a state of protracted, constant excitation. When treatment with anti-bacterial preparations is effective, the focus of infection is eliminated, simultaneously the transmission of impulses into the central nervous system ceases and its protracted and constant excitation ends. The dominant of the bronchial asthma fades away, the attacks of bronchial asthma stop, and a remission sets in.

If, however, the focus of infection proved to be penicillin- or sulfanilamide-resistant, the protracted, constant excitation of the central nervous system remained, as well as the dominant, and the attacks continued with former intensity. By applying streptomycin, we succeeded in a number of cases in eliminating such foci of infection and thereby ending the protracted constant excitation of the central nervous system; the dominant of bronchial asthma faded away and a prolonged remission set in.

Hence, anti-bacterial preparations provide us with a powerful therapeutical remedy enabling us to treat patients suffering from bronchial asthma, from an infection of the respiratory organs and an asthmatic state, and to achieve a lasting remission between attacks. The treatment of bronchial asthma patients with anti-bacterial therapy should be recommended in cases of an infection focus in the respiratory organs—the lungs or bronchi.

2. PROTECTIVE THERAPY

The treatment of bronchial asthma patients with novocaine began as far back as 1907. In his doctorate thesis on "The Method of Treatment by Means of Intratracheal Infusions," A. Y. Galebsky was the first to point out that intratracheal injections of liquid drugs made to patients affected with bronchial asthma lead to their recovery, or, at least, considerably reduce severe asthma attacks. A report by Ephraim received from abroad on the effective treatment of bronchial asthma patients with injections of novocaine solutions into the trachea date back to the same period.

We found no data in Russian literature covering the period of 1907-1935 on the treatment of bronchial asthma with novocaine. It was only in 1935 that V. Yaroslavsky made public four cases of recovery of bronchial asthma patients after treatment with intratracheal injections of a 2 per cent solution of novocaine.

The technique of injecting the solution was as follows. After a preliminary anaesthesia of the nasal mucosa by means of a 5 per cent cocaine solution, and of the trachea by means of a 1 per cent cocaine solution, 10-20 ml. of a novocaine solution plus 1.0 ml. of a 1:1000 adrenaline solution were injected into the trachea with a special laryngeal syringe. The patient received from three to ten intratracheal injections in the course of 15-30 days. The course of treatment was repeated three or four months later. In 1939, M. A. Levitin and K. I. Sheinyuk published data obtained as a result of a similar treatment of 18 bronchial asthma patients. In fifteen cases favourable results were obtained and in three cases no marked effect was achieved.

That same year M. Izrael treated patients suffering from bronchial asthma with 0.25 per cent novocaine based on a saline solution which was injected intravenously in doses from 5 to 10 ml. The number of injections for the course of treatment ranged from 5 to 24. When the solution was injected, the patients became slightly indisposed and suf-

fered from dizziness and numbness in the arms. However, these sensations quickly passed.

After several injections the general condition of the patients improved; they slept well, were calm, and the attacks ceased. Out of 37 patients a remission lasting one-two years set in in 20 cases; in 13 cases an improvement was recorded and in four the condition remained unchanged. The treatment lasted from one to five months.

At the same time A. V. Vishnevsky's method was introduced for the treatment of bronchial asthma patients with novocaine block. A. Y. Bogdasarov and N. V. Domrachev who applied this method obtained good results.

We treated patients affected with bronchial asthma with a 0.25 per cent novocaine solution which was administered in various ways: into the hypodermic tissue and the muscles of the neck by means of a vago-sympathetic unilateral or bilateral jugular block after A. V. Vishnevsky, or by means of intracutaneous block after A. D. Speransky. In addition, a novocaine solution was injected intravenously and intrabronchially as an independent method of treatment and also when using bronchography. The treatment of patients by means of A. V. Vishnevsky's jugular vago-sympathetic and lumbar block method and A. D. Speransky's intracutaneous block was effected by us in collaboration with Assistant Professor A. V. Afanasyeva.

We have at our disposal observations on 106 patients (33 men and 73 women). An acute infection in the respiratory tract was recorded in 16 cases; 17 patients were free from any infection in the respiratory tract. In 73 cases complications were recorded—chronic vesicular emphysema of the lungs, chronic pneumonia, etc. The age groups were as follows: 20 years and under—18 patients; between 21 and 30—16; 31 and 40—34; 41 and 50—25; 51 and over—13 patients.

The disease began at different ages. Fifteen patients fell ill at the age of 20 or under; 28—at the age of 21-30;

36—at the age of 31-40; 19—at the age of 41-50; 8 patients fell ill at the age of 51 or over.

The patients were grouped according to the duration of the disease in the following way: 5 years or less—18 patients; from 6 to 10 years—15; from 11 to 15 years—28; from 16 to 20 years—16; from 21 to 25 years—20; over 25 years—9 patients.

This shows that treatment was administered to patients who had long suffered from bronchial asthma and who had been treated for a considerable time at different dispensaries and hospitals.

1. The vago-sympathetic jugular block was administered strictly in accordance with the technique described by A. V. Vishnevsky. In most cases a unilateral vago-sympathetic block was administered in the right and left sides alternately.

A bilateral block was carried out in the case of 19 patients and a unilateral block in 13 cases. Altogether 42 bilateral and 138 unilateral blocks were administered. From 40 to 50 ml. of 0.5 per cent novocaine solution were used in the unilateral blocks; in bilateral blocks a greater quantity of novocaine (80-100 ml.) was used. As soon as novocaine was introduced, Horner's syndrome (constriction of the pupil, sinking in of the eyeball and narrowing of the palpebral fissure) appeared in almost every patient, which pointed to a block of the sympathetic trunk. If swallowing became difficult and the voice changed, this served as indication of a block of the vagus. In the majority of patients these symptoms continued for 1.5-3 hours, and sometimes even longer.

When a unilateral block was applied, no complications followed. Only in a few instances was pain recorded in the site of the injection, which lasted for about a day.

In two cases a weakening of the pulse and severe dyspnea were observed when a bilateral block was administered. These passed in 30 or 40 minutes, requiring, however, the administration of cardiotonics and oxygen. The influence

exercised by the unilateral and bilateral vago-sympathetic block on the activity of the heart and lungs was ascertained by means of electrocardiograms taken before and after the block. A change in the electrocardiogram was observed after a bilateral vago-sympathetic block. The wave increased and remained upward in all leads.

The respiratory function was investigated by means of a spirographic curve: the findings showed that the central nervous system had ceased to influence and exercise control over the respiratory organs, which was manifest in the changes in the spirographic curve with regard to the decelerated frequency of the rhythm of respiration, the greater depth of respiration, and the increase in the vital capacity and respiratory coefficient.

The blocks were administered with intervals of 7-10 days. As a rule, one block proved to be insufficient to produce a curative effect. Repeated blocks are considered indispensable by other Soviet authors as well (Y. A. Bogdasarov, 1941; Y. D. Evzerov, 1935; P. A. Panikov, 1938; A. N. Kryukov and D. S. Vaza, 1936; M. V. Tulenkov and P. A. Sorokin, 1938; N. V. Domrachev, 1938).

After a block, administered during an attack or asthmatic state, in 40 instances dyspnea and the asthmatic state disappeared in 10-15 minutes. The patients were able to breathe freely and deeply. Quite often they fell asleep—evidently from the effect of novocaine on the central nervous system. The remission lasted from 1.5 to 3 hours and in some cases up to 24 hours. Then attacks of bronchial asthma reappeared or an asthmatic state set in. The patients usually noted that the recurrent attacks or asthmatic state were less intensive, and the intervals between the attacks longer. Drugs which previously produced no effect at all (adrenaline, for example) again acquired their capacity of quickly arresting attacks. The amount of sputum decreased, and the general condition of the patients showed marked improvement; they had a better appetite and gained weight.

The results of the therapeutical application of the novo-

caine vago-sympathetic jugular block, administered according to the afore-mentioned method, were as follows:

1) In 10 cases the attacks ceased and did not recur for a period of 6-12 months.

2) In 13 cases there were no attacks during 3-6 months.

3) In 15 cases the attacks became less intensive and of shorter duration.

4) In 11 cases no visible effect was produced.

In no case was recovery produced.

II. Twelve patients were treated with lumbar novocaine block. During treatment we observed a quickening of the pulse by 20-30 strokes a minute and an increase in the frequency of respiration by 5 to 12 times a minute. The change in the maximum blood pressure ranged from 5 to 20 mm. Hg tending more often to increase; the minimum blood pressure remained unchanged. The data of the electrocardiogram, obtained before and after the block, showed no change. If the block was administered during an asthmatic state the latter continued, and the patient only felt pain where the novocaine solution was injected.

The results of the therapeutical application of the novocaine lumbar block, administered according to the above method, were as follows:

1) In 3 cases the attacks ceased for nearly six months.

2) In 3 cases the general state and appetite improved and a change was recorded in the nature of the attacks: the latter became less pronounced, adrenaline and ephedrin, which hitherto had no effect, now quickly stopped the attacks.

3) No curative effect was obtained in 6 cases where the patients had suffered from the disease for over 15 years and had toxic-infection foci in the lungs.

III. A. D. Speransky's method of intracutaneous novocaine block was applied in 18 cases. The block was administered by injecting into the skin itself from 120 to 150 ml. of a 0.5 per cent novocaine solution. Novocaine injections were administered over a rhomboid area limited by lines stretch-

ing from the spines of the fourth cervical and the fifth thoracic vertebra to the angles of the scapulae.

When the block was administered, changes in the pulse, breathing and blood pressure were recorded similar to those observed during the vago-sympathetic lumbar block. No changes in the electrocardiogram or spirogram were registered.

After the block had been applied, the pain in the site where the solution of novocaine was injected persisted for several hours.

In order to obtain the desired therapeutic effect from three to five blocks were required with intervals of 5-7 days.

The results of the therapeutic application of the intracutaneous novocaine block, administered according to the above method, were as follows:

1) In three cases the attacks ceased for a duration of 6-9 months.

2) In six cases there were no attacks for about six months.

3) In five cases an improvement was recorded: the attacks continued, but they were less vigorous and lasted less.

4) In four cases no therapeutic effect was obtained, since all the patients had been affected with the disease for a long time and suffered from a chronic infection of the bronchi and lungs.

IV. In 27 cases several kinds of blocks were applied. At first a jugular unilateral vago-sympathetic block was administered according to A. V. Vishnevsky's method, followed in 5-7 days by an intracutaneous block according to A. D. Speransky's method, and then these were alternated. Altogether 151 blocks were applied, i.e., an average of five or six blocks to each patient.

The final results were more effective than those obtained when applying separately the intracutaneous block according to A. D. Speransky's method or A. V. Vishnevsky's vago-sympathetic jugular method. The results of the therapeutic application of the several kinds of blocks administered according to the above methods were as follows:

1) In eight cases the attacks ceased for over six months;
2) In ten cases—for nearly six months;
3) In six cases an improvement was recorded;
4) In three cases the condition remained unchanged.

V. An intravenous injection of a 0.25 per cent novocaine solution was administered to 27 patients.

Injections of novocaine should begin with small doses so as to avoid any collateral phenomena, as recorded in the case of one of our patients. On the first day from 3 to 4 ml. of the solution were injected and on each succeeding day the quantity was increased by 1 ml. until it reached 10 ml. Then, with each subsequent injection it was reduced by 1 ml. and brought down to the initial figure.

The course of treatment consisted of 15-20 injections.

When the novocaine solution was injected without any attending attack, the patients felt indisposed, weak and giddy, but, as a rule, all these sensations passed away in 5-10 minutes, and a general improvement set in.

After an intravenous injection of novocaine the patients felt drowsy and in a few minutes fell asleep, the sleep lasting from one to five hours. Our patients fell asleep most frequently when 3 or 4 ml. of a 0.25 per cent novocaine solution was injected; when the dose was increased, the sleep became more profound and of greater duration. When decreased, the patients slept until the injection of novocaine was stopped. This phenomenon is also observed when novocaine is administered by other methods—further confirmation of the fact that novocaine solutions, being soaked into the blood, exercise an influence similar to that observed when it is injected intravenously.

When a novocaine solution was injected during an asthmatic state (most frequently at the beginning of the treatment) the patients felt an abatement of asphyxia and heaviness in the chest. A few minutes after the injection they were able to breathe freely for 2 or 3 hours, and then an asthmatic state set in again. Each subsequent injection of a novocaine solution lengthened the period free from any

asthmatic state or attack. By the time 7-9 injections were administered the asthmatic state disappeared in patients who did not suffer from any complications. In the case of patients who suffered from complications—a lasting chronic infection of the respiratory tract and a chronic emphysema of the lungs—the disappearance of the asthmatic state and attacks was less pronounced.

The results of the therapeutic application of a 0.25 per cent novocaine solution, administered intravenously according to the above methods, were as follows:

1) In 8 cases the attacks ceased for a year or longer;
2) In 8 cases the attacks ceased for over six months;
3) In 13 cases there were no attacks for a period of three-six months;
4) In 3 patients suffering from infection foci in the lungs the bronchial asthma attacks continued and there was no improvement of the general condition.

VI. Bronchography was applied in our clinic by Dr. D. M. Zlydnikov to 100 patients suffering from bronchial asthma.

When the patient was prepared for bronchography, in order to annul the cough reflex, the nasal mucosa, nasopharynx and larynx were treated with a 2-5 per cent cocaine solution and a 0.25 per cent novocaine solution followed by iodolipole was injected into the trachea, bronchi and lungs.

We consider bronchography a diagnostic method. The curative effect which is obtained with bronchography depends on the action of cocaine and novocaine on the receptors of the respiratory tract mucous membrane. In the final analysis, the bronchographic method causes a block of the sensitive receptors of the mucous membrane with novocaine and iodolipole acting simultaneously on them.

Observations showed a general improvement in 46 patients after a single application of bronchography.

It is worth noting that the condition of some patients improved a few hours after the application of bronchography, and in most cases within the first day.

The therapeutic results obtained in bronchial asthma patients were as follows:

1) In 37 cases the attacks ceased for a period of one-three months;

2) In the case of 36 patients suffering from chronic bronchitis and chronic vesicular emphysema of the lungs, the attacks continued, but were of less pronounced vigour and duration;

3) In 24 cases bronchography was applied during a remission;

4) In three cases of chronic bronchitis and chronic vesicular emphysema of the lungs, the attacks continued, and no improvement was recorded.

It should be noted that such drugs as ephedrin, adrenaline, etc., which produced no effect or acted weakly before bronchography was applied, began to act more effectively and for a longer period after its application.

Table 2 gives summary data on the various kinds of blocks, on bronchography and the treatment of patients with intravenous injections of novocaine solutions.

Table 2 shows that the best results were obtained with intravenous injections of novocaine solutions.

To sum up, this is how the mechanism of action of novocaine presented itself to us in each case:

1. When A. V. Vishnevsky's method of the vago-sympathetic jugular block is applied, novocaine acts on the central nervous system directly through the blood or through the nerve trunks and spinal cord ganglia. When this kind of block is instituted, from 0.12 to 0.4 gm. of novocaine are injected. The novocaine gradually penetrates into the blood, and, in addition, acts, in the site of the block, anaesthetically on the sections of the nerve trunks and the receptors of spinal cord and vagus nerves. The introduction of the vago-sympathetic block causes an interruption in the reflex arc, thereby inhibiting the transmission of the impulses from the periphery, i.e., from the lungs, to the central nervous system and leading to the appearance of new impulses in the site

Table 2

Method of Treatment	Number of patients	Results of treatment					Total number of blocks administered
		No attacks			Improvements	No change	
		Over a year	Over 6 months	Up to 6 months			
Jugular vago-sympathetic block according to A. V. Vishnevsky's method: Bilateral	19	—	2	5	6	6	42
Jugular vago-sympathetic block according to A. V. Vishnevsky's method: Unilateral	30	—	8	8	9	5	138
Lumbar vago-sympathetic block according to A. V. Vishnevsky's method	12	—	—	3	3	6	36
Intracutaneous block according to A. D. Speransky's method	18	—	3	6	5	4	42
Different blocks administered alternately	27	—	8	10	6	3	151
Intravenous injection of novocaine	27	3	8	13	—	3	—

of the anaesthesia of the nerve—in its central and peripheral sections.

N. E. Vvedensky, an outstanding Russian physiologist, believed that narcosis of the nerve is an active state, a state of excitation. This excitation differs, however, from excitation as it is generally understood: being a secluded excitation confined to the point of its origin and incapable of spreading along the nerve, it is stable and unvacilating. Along with the changes in the section under anaesthesia changes may be found in the sections of the nerve adjoining the parabiotic region.

N. E. Vvedensky has established that when irritability is reduced in the parabiotic section, the normal section of

the nerve adjoining it displays, on the contrary, greater irritability. During complete parabiosis any additional stimulation of the parabiotic region, coming from any point throughout the length of the nerve, causes a further intensification of irritability in the adjoining normal sections and a still greater weakening of the functional properties within the parabiotic section itself.

N. E. Vvedensky considered this phenomenon to be fresh evidence of the fact that parabiosis is a state of peculiar excitation.

2. When A. D. Speransky's intracutaneous block is administered, novocaine acts directly on the cutaneous receptors and those of the cutaneous veins, and then through the spinal cord on the central nervous system; in addition, novocaine acts on the central nervous system when it is sucked into the blood.

Hence, when A. D. Speransky's intracutaneous block is applied, novocaine acts on the central nervous system in two ways: directly through the blood, and through the spinal cord ganglia.

3. When a novocaine lumbar block is administered, the anaesthetics act on the nerve receptors of the spinal cord ganglia and the receptors of the vegetative nervous system located in the perirenal cellular tissue, as well as directly on the central nervous system when novocaine solutions are sucked into the blood.

4. When cocaine and novocaine solutions are infused into the nasal cavity, nasopharynx and bronchus, anaesthesia of the receptors of their mucous membrane takes place and their communication with the central nervous system is interrupted. Furthermore, the novocaine and cocaine solutions, when sucked into the blood, act on the central nervous system. When bronchography is applied, the action of novocaine and cocaine should be considered as the basic, and the injection of iodine in the shape of iodolipol, a 40 per cent oil suspension, a secondary factor which acts anticeptically on the infection localized in the bronchi and

lungs. The quantity of novocaine and cocaine injected into the body during bronchography is quite sufficient to produce a definite therapeutic effect.

5. A 0.25 per cent novocaine solution, injected intravenously, acts through the chemoreceptors of the vascular system and the central nervous system.

The problem of what parts of the central nervous system are affected by the action of novocaine should be considered in connection with the changes occurring in the central nervous system of patients suffering from bronchial asthma, i.e., in connection with the problem as to the origin of "foci of stagnant excitation" according to I. P. Pavlov, or the dominant foci of greater excitability according to A. A. Ukhtomsky.

We believe that the foci of greater excitability—the pathological dominant of bronchial asthma—are formed in the central nervous system where the working constellations have long ago firmly taken shape (A. A. Ukhtomsky): in the medulla, in its bulbar link, in the cerebral subcortex and cortex.

Only the localization of the dominant in the cerebral cortex can explain the fact that bronchial asthma is caused by negative or positive emotions, or that its attacks are brought about by visual, auditory and olfactory impressions.

In conclusion, it should be noted that novocaine treatment of patients suffering from bronchial asthma is of great practical and theoretical interest. However different the methods of injecting novocaine solutions may be, it is the inflow of novocaine into the blood stream and its direct action on the chemoreceptors of the vessels and on the central nervous system that matters most. With the application of various methods of treatment, additional factors arise affecting the peripheral receptors of the mucous membrane of the respiratory tract (intratracheal method), cutaneous receptors and spinal cord ganglia innerving the lungs (A. D. Speransky's method of intracutaneous block), and the nerve trunks connecting the central nervous system

with the lungs (A. V. Vishnevsky's method of vago-sympathetic block).

Thus the following interdependence is established in treating bronchial asthma patients with novocaine:

1. Anaesthetizing the receptors of the nasal, tracheal and bronchus mucosa with novocaine and cocaine solutions interrupts their connections with the central nervous system, with result that the asthmatic state and attacks of bronchial asthma pass away.

2. In cases of bilateral jugular vago-sympathetic blocks the direct connection with the central nervous system is likewise interrupted, and a remission sets in.

3. Intravenous injections of novocaine solutions, after which a remission also sets in, have proved to be a most effective method of treatment. Subcutaneous, intravenous and intrabronchial injections of novocaine solutions made the patients drowsy, and in some cases sent them to sleep. Then followed an improvement in the general condition.

The above shows that novocaine acts mainly on the central nervous system, and that the beginning of the attacks of bronchial asthma and of the asthmatic state is directly dependent on the condition of the central nervous system. We consider treatment with novocaine a pathogenetic method of treating bronchial asthma through its action on the central nervous system, chiefly on the cerebral cortex and the parts of the central nervous system subordinated to it.

In summing up, the following conclusions can be drawn.

1. Intravenous injections of a 0.25 per cent novocaine solution are most effective in treating patients suffering from bronchial asthma, the course of treatment consisting of 15-20 infusions.

2. Next in importance are intratracheal injections of novocaine solutions which are applied simultaneously with the treatment of the mucous membrane of the nose, nasopharynx and trachea with novocaine and cocaine solutions administered in the same way as in bronchography.

3. Third in importance rank A. V. Vishnevsky's and A. D. Speransky's methods of treatment by means of bilateral jugular vago-sympathetic and intracutaneous blocks.

4. Treatment with novocaine should be recommended in all cases of bronchial asthma, and particularly when it is attended with prolonged persistent attacks.

Hydrochloric acid cocaine has been used to treat bronchial asthma since the last century.

The nasal mucosa and that of the back wall of the gullet and larynx were treated with 2-10 per cent cocaine solutions. Cocaine belongs to the liquids recommended for the irrigation of the nasal mucosa, pharynx and trachea of asthmatics, in combination with adrenaline, menthol or other drugs.

As mentioned above, cocaine solutions were administered to 100 patients to anaesthetize the nasal mucosa, pharynx, larynx and trachea when bronchography was applied, and to 19 patients as an independent method of treatment.

When applied locally, cocaine reduces the secretion of the mucous membrane glands as well as its swelling. Under the influence of cocaine a paralysis occurs of the endings of the sensitive nerves of the nasal, pharynx and larynx mucosa, and anaesthesia sets in which interrupts the reflex arc leading from the mucous membrane into the central nervous system.

The treatment of the mucous membranes is also accompanied by a general effect on the body, on the central nervous system: "The action of cocaine," wrote N. P. Kravkov, "is very difficult to analyze, since simultaneously with the excitation of some parts of the central nervous system, in particular of the middle brain and medulla, a paralysis of other parts sets in, or, the excitation of a certain part is followed by its rapid paralysis, etc."

We have been favourably impressed with the action of cocaine on patients affected with bronchial asthma.

Our observations prove the effectiveness of novocaine and cocaine when protective therapy of the central nervous

system is administered to patients suffering from bronchial asthma. These preparations were designed to act upon the interoceptors with a view to interrupting the reflex arc.

It was ascertained that when bilateral vago-sympathetic blocks or anaesthesia of the nasal, tracheal or bronchus mucous membrane were administered the bronchial asthma attacks stopped during the action of novocaine.

Thus, by protecting the central nervous system from the factors which cause its prolonged stimulation so that it no longer reacts on the exogenous and endogenous impulses that reach it, it is possible to obtain a direct therapeutic effect and subsequently to consolidate it in the form of a long remission between attacks.

It should be noted that when infection is detected in patients, pharmacological treatment should be aimed at abating along the respiratory tract the inflammatory phenomena which make for the sensitization of the body. In case of lung or heart complications a suitable therapy should be applied to promote their normal functioning.

We treated ten of our bronchial asthma patients with barbiturates: luminal, veronal and other preparations which were administered in doses of 0.05 gm. two or three times a day; at night the patients received larger doses, up to 0.1 gm. of veronal was applied in doses of 0.3-0.5 gm. two or three times a day, the daily amount totalling 1.5 gm. As a rule, the patients went off to sleep after taking 0.1 gm. of luminal or 0.5 gm. of veronal, but in the night they awoke from an attack of bronchial asthma. In seven patients the attacks were checked with difficulty by means of 1 mg. of adrenaline. It often became necessary simultaneously to administer a dose of 0.2 gm. of caffeine or a repeated dose of 1 mg. of adrenaline. The attacks were acute, the sputum was difficult to eject and always abundant.

During the remission a certain effect was obtained with luminal and veronal, and in three patients the treatment proved successful.

We explain the deterioration in the condition of a group

of patients in an asthmatic state suffering from complications in the form of chronic emphysema of the lungs and myofibrosis of the heart, or of patients suffering from an acute infection of the respiratory tract, by a drastic weakening of the higher nervous activity.

Attacks during sleep are associated with the removal of the control function of the cerebral cortex and with a higher tone of the parasympathetic part of the vegetative nervous system. Conditions arise when the bronchospasm and the secretion of mucilage into the lumen of the bronchi are intensified; the sputum does not evacuate itself from the lungs; it accumulates in the lumens of the bronchi and clogs them, adding to the stimulation of the interoceptors of the mucous membrane of the bronchi. The impulses coming from the interoceptors of the bronchi, in their turn, sustain the dominant, producing a reflex attack of bronchial asthma. These two factors are especially pronounced in patients suffering from complications of bronchial asthma which are accompanied by an infection of the respiratory organs.

"Inhibition," says I. P. Pavlov, "which together with the excitation constantly takes part in the diverse activity of the animal in its wakeful state, also guards the extremely reactive cells of the organism, the cells of the cerebral cortex; it protects them from highly strenuous work under the action of very strong stimuli, or even under the prolonged repetition of weak stimuli; it also ensures the necessary rest for cells in the form of sleep after their daily normal work."

According to I. P. Pavlov, sleep is the result of a diffused inhibition, and is a protective, defensive factor, guarding the central nervous system from excessive fatigue and extreme exhaustion of the nervous tissues resulting from a pathological process. Sleep reacts favourably on the heightened excitability of the cortex and subcortex and ensures a proper level of the restorative processes.

"Protective inhibition," wrote A. G. Ivanov-Smolensky,

"deepened or caused by sleep therapy, restores both the normal work of the cerebral cortex and its disturbed interrelations with the underlying parts of the central nervous system, and at the same time helps to bring back to normal the central regulation of the vegetative functions and to eliminate phenomena of their dissociation."

It follows from the above that induced sleep cannot produce favourable results in patients affected with bronchial asthma and suffering at the moment from an attack. The pronounced process of inhibition to which they are subjected and which is accompanied by a drastically reduced higher nervous activity does not yield to the normalizing effect of sleep; on the contrary, it grows more serious.

We, therefore, believe that pharmacological sleep should only be recommended to patients suffering from bronchial asthma who are in a state of remission and when there are neither infection foci in the lungs nor complications.

Artificial sleep should be considered as contraindicated for patients suffering from bronchial asthma and showing infection foci in the respiratory organs and particularly complications such as: chronic vesicular emphysema of the lungs or myofibrosis of the heart attended with insufficiency of the right ventricle, etc.

Consequently, our attempts to treat bronchial asthma patients with pharmacological sleep proved of no avail, though these were made strictly individually and with due regard to the specific conditions of the patients.

3. PSYCHOTHERAPY

The problem of treating patients suffering from bronchial asthma with psychotherapy has not as yet been sufficiently investigated.

The data published so far only point to isolated instances of good, though transitory results, obtained with this kind of treatment.

V. M. Bekhterev, a prominent Russian physician, said: "Treatment by suggestion, skilfully administered in the waking period of the patient, is a highly effective curative remedy which should never be ignored by physicians."

M. V. Chernorutsky wrote that the elements of psychotherapy should generally be applied by all physicians; he suggested a number of organizational measures in the field of psychotherapy: the instruction of psychotherapy and general clinical psychopathology at medical institutes, and the elaboration of methods of examining patients. During these examinations particular attention should be paid to the anamnesis of the patient with which psychotherapy should begin. Every medical establishment (hospital, polyclinic) should have a calming effect on the patient by its very appearance (comfort, cleanliness, cosiness) and regulations.

N. F. Golubov recommends that psychotherapy, along with other methods, should be employed in the treatment of bronchial asthma patients. He suggests that patients be advised to lead a proper life and follow the regimen and course of treatment prescribed by the physician.

Psychotherapy can only be successful when close contact is maintained with the patient. This can be conveniently begun during the examination of the patient. The latter should be inspired with confidence in the doctor and assured of his recovery.

The doctor's talk should be consistent with the patient's intellectual development. He should be given an opportunity to speak his mind and to apply to the doctor for an explanation of every incomprehensible question relevant to the disease.

The first task of psychotherapy is to encourage the patient, to restore his self-confidence and allay his fears. As is known, psychotherapy has its own physiological foundation which has been expounded in I. P. Pavlov's teaching on the higher nervous activity.

"Words are to man as real a conditioned stimulant as all the others, which he has in common with animals," he wrote. "But at the same time they are so capacious as no other and cannot in this respect be compared, in terms of quantity or quality, to the animals' conditioned stimulants. Owing to the adults' entire past, words are associated with all the external and internal stimulations that come to the cerebral cortex; they can signal and substitute them entirely and can, therefore, call forth all those actions and reactions of the organism which are due to those stimulations. Hence suggestion is the most simplified and most typical conditioned reflex of man."

From the physiological point of view psychotherapy is "conditioned functional therapy which reacts on the cortex dynamics and, through it, on the subcortical and vegetative parts of the central nervous system."

At the present time psychotherapy methods may be subdivided into two main groups: 1) psychic treatment administered against the background of a hypnotic state accompanied by inhibition of the second signal system; 2) against the background of an active state of the cortex, with the activity of the second signal system remaining unchanged.

In treating our patients, Dr. P. I. Boole applied psychotherapy along with other methods. Psychotherapy was particularly recommended in cases when conventional therapy was of no avail. The choice of any particular method of treatment is left to the physician who decides how best to influence the psychics of the given patient from the data at his command.

"The words of the person," says Pavlov, "who begins to hypnotize the individual in question—given a certain degree of inhibition developing in the cortex of the hemispheres—by concentrating stimulation in a specific limited area according to the general law, at the same time cause a naturally deep external inhibition (as in the case I have just pointed out) throughout the remaining mass of the hemispheres and thus preclude any competing effect by

any of the other traces of stimulation, present or past. This accounts for the great, all but irresistible force of suggestion as a stimulant during and even after hypnosis. Words retain their effect after hypnosis, too, remaining intact and independent from other stimulants, as having not been connected with them at the moment when they were first applied to the cortex."

The comprehensiveness of the word makes it clear why so many diverse exertions aimed at man's both external and internal world can be provoked by suggestion in a hypnotized man.

In our current practical work we chose the method of suggestive psychotherapy (suggestion during hypnosis) out of the vast and complex arsenal of psychotherapeutic remedies and methods. The choice was so made chiefly because hypnosis is now a well-investigated phenomenon and, as shown above, its mechanism is disclosed.

We have at our disposal observations on 15 patients. Various methods were applied without any subsequent improvement—the attacks of bronchial asthma continued. These recurrent attacks were due to severe psychic traumas and shocks.

The paradox is well known that strong social shocks cause prolonged lucid intervals in the course of bronchial asthma. Instead of aggravating the condition of the patient, these unfavourable factors eliminated the attacks. In some of our patients the attacks arose in line with the principle of "pathological conditioned reflexes." Having once arisen under the influence of toxi-infectious or allergic causes, the asthmatic attack was subsequently associated with definite surroundings, a certain odour or a definite emotional state. When the given situation was repeated, a conditioned reflex was developed which regularly resulted in an attack. An example worth citing is the case of a paper rose which, when shown on a screen, caused an attack of bronchial asthma in a patient through the visual analyser, though the flower had no odour. A patient in our clinic who had looked

through some publications on bronchial asthma (the neighbour on the bed next to her being a physician) began to suffer from attacks as a result of various odours, though formerly the irritation of the olfactory analysers played no part in the appearance of attacks.

Our patients included two men and thirteen women. As a rule individual seances of hypnotherapy were practised.

The number of seances varied in accordance with the time an improvement set in in the patient's condition, with the duration of his stay in the clinic and his reaction towards the course of treatment. The longest course consisted of 30 seances, and the shortest of 10. The results of treatment were recorded by comparing the number of attacks during the week and in the course of the day before and after hypnotherapy treatment. Usually, it was the patient himself who soon felt an improvement; the information supplied by the doctors was particularly valuable. In the case of two patients hypnotherapy produced excellent, in three good and in five satisfactory results; in five cases the treatment was ineffective and the attacks continued. It should be noted that in the last instance it proved impossible to produce a sufficiently profound hypnotic state. Below are the clinical cases of some of our patients.

Patient P. Kh., female, aged 42, entered the hospital therapeutical clinic on October 2, 1951. She fell ill with bronchial asthma in the Urals, during evacuation, at the age of 34. The first attack was preceded by bronchitis which lasted about a year, following a psychic trauma. She was treated with hypnosis; altogether 18 seances were administered. For eight years the patient enjoyed good health. In 1946, she returned to Leningrad and began to work as a teacher. The bronchial asthma attacks recurred early in 1949, after influenza and exacerbated chronic asthmatic bronchitis. The patient was treated in the hospital therapeutical clinic with aero-ionization with a negative charge. After 30 seances good therapeutical results were obtained, and there were no attacks for eight months. In December 1949, the patient sustained another psychic trauma. The attacks returned, but did not trouble the patient much: only once or twice a month. In July 1951, she had influenza and bronchitis, followed by bronchial asthma attacks which in September turned into an asthmatic state.

On October 2 the patient was taken to the clinic for stationary treatment. She was given a course of treatment with aero-ionization with a negative charge, receiving 0.05 gm. of ephedrin three times a day and injections of 1 ml. of a 1:1000 adrenaline solution from one to ten times a day.

Two spells of exacerbation of her asthmatic state were recorded in the clinic—at the end of October and in November.

Hypnosis treatment of the patient was begun in November. Three or four seances stopped the attacks, five or six brought about a good general improvement; the patient ate with appetite, slept better and put on three kilogrammes of weight. In the course of treatment the patient yielded well to hypnotism: she did not awake while in a hypnotic state, replied to questions and followed instructions.

It was easy to suggest various positive or negative emotions to the patient, or to provoke an attack of bronchial asthma. As soon as she awakened from the hypnotic state, complete amnesia set in.

The general condition of the patient was excellent. She thanked the doctor and said she felt quite well and cheerful after every seance. The course of treatment comprised 20 seances. The patient was discharged in a good condition.

Patient A. V., female, aged 39, began to receive dispensary treatment at the hospital therapeutical clinic on October 1, 1951. She fell ill with bronchial asthma when 37 years of age, without any cause apparent to the patient.

The patient worked for many years at a textile mill and was periodically ill with exacerbated chronic bronchitis.

In 1941, she and her two children were evacuated from Leningrad to Yaroslavl Region where she stayed till 1946.

Throughout that period her life was hard. She was also worried about her soldier husband from whom she had heard nothing since his departure for the front. In 1946, she was notified of her husband's death. In 1949, attacks occurred once or twice a month. That same year she was treated in Kislovodsk and felt better. In January 1950, she had influenza which was followed by severe attacks of bronchial asthma.

In January and February a protracted asthmatic state was recorded; throughout that year she had repeated attacks once or twice a month. In January 1951, after a further aggravated infection of the respiratory tract, the attacks became more severe. This condition lasted nine months.

After three or four hypnotic seances the patient's condition rapidly improved and no attacks were recorded after the fourth seance (the patient's living conditions remained the same as before treatment). She slept well and in four weeks put on three kilogrammes of weight.

The spasms in the windpipe disappeared, and she no longer wept or fretted.

When treatment with hypnosis was applied, profound sleep, resembling normal physiological sleep, set in. During hypnosis it was possible to suggest emotions of a negative or positive character. When negative emotions were suggested, grief and tears appeared on the patient's face. When positive emotions were suggested her face expressed joy, and she laughed.

With the patient in a hypnotic state it was possible to provoke a typical attack of bronchial asthma when a count of three was taken. It should be noted that a more serious attack followed after a break of one or two minutes without any additional suggestion. After a count of five the attack instantly disappeared. Attacks were likewise checked with a subcutaneous injection of 1 ml. of a 1:1000 adrenaline solution or by suggestions that adrenaline had been administered. Altogether 15 hypnotic seances were applied.

The patient felt well and fit.

We were also interested in the following question: is it possible to provoke an attack of bronchial asthma by means of a corresponding verbal suggestion? We made the test in five cases, with the patients' consent. They were told: "Now, when I count three, your breathing shall change and a typical attack of asthma shall develop. I am counting—one, two, three—the attack has begun." A typical attack of bronchial asthma began with unfailing regularity, accompanied by an excretion of the same light sputum as in the case of ordinary attacks.

During a suggested attack a spirogram was recorded of the patient's respiration with Knipping's apparatus. The spirograms obtained during a suggested attack did not differ from those recorded during an ordinary attack or an asthmatic state. In both cases there appeared to be a lengthening of the expiration phase, lesser vital capacity of the lungs, an increased respiratory rate and smaller minute volume. The attacks artificially provoked by suggestion were easily removed by counter-suggestion: "Now, at the count of five, your respiration shall change for the better, and the attacks shall cease. I am counting—one, two ... your respiration has become regular, you are

breathing easily and freely ... three, four ... the attack is passing ... five—the attack has passed." The attack ceased with amazing precision, and the patient went on sleeping with his breathing even and calm—he was in a hypnotic state. This was verified by suggesting positive or negative emotions to the patient and by simultaneously recording spirographic changes. These curves radically differed from those obtained in the same case during bronchial asthma attacks.

Hence, by means of verbal signals through the auditory analyser it is possible to provoke in a bronchial asthma patient the same response of the cerebral cortex, subcortex and vegetative centres, with subsequent pathological changes in the respiratory organs (spasms of the bronchus muscles, hypersecretion), as in the case of an ordinary bronchial asthma attack.

It should, however, be noted that bronchial asthma attacks can only be provoked in patients who lapse into a sufficiently profound hypnotic state and who possess a developed conditioned reflex mechanism of bronchial asthma attacks. We failed to bring about bronchial asthma attacks in patients affected with other diseases, or in healthy persons.

Thus an attack of bronchial asthma can arise either as an unconditioned reflex in response to external or internal pathogenic stimulations or as a conditioned reflex of the first or the second signal system.

On the other hand, an attack of bronchial asthma that has already arisen can be eliminated by the same hypnotic suggestion which in this case acts as a verbal conditioned inhibition.

It has been ascertained that a word can act as the conditioned stimulating agent provoking an attack of bronchial asthma. In one case the word was "Yalta" which our patient associated with the health resort in the Crimea where she had had her first attack. It was found that a bronchial asthma attack can also be prevented by a word.

Thus hypnosuggestive therapy, when skilfully applied, is an effective method of treating patients suffering from bronchial asthma. Successful treatment depends on the patient and on the individual qualities of the physician, the psychotherapeutist, who should possess skill and be familiar with the teaching of I. P. Pavlov and S. P. Botkin.

4. DESENSITIZING THERAPY

In the last 15 or 20 years great attention has been given in Soviet medical literature to the treatment of bronchial asthma by aero-ionization with a negative charge; unfortunately, no indications exist as to the possible effect of collateral physical agents (electric field, gaseous substances, ozone, nitrogen oxides, etc.) which appear simultaneously with the generation of aero-ions (I. E. Landsman, N. S. Zvonitsky, A. N. Obrosov, B. M. Prozorovsky, E. I. Pasynkov, F. E. Obrant and others).

In 1936, L. L. Vasilyev, for the first time in the Soviet Union, applied aero-ionization with a negative charge to treat a group of patients suffering from bronchial asthma. Light negatively charged aero-ions were obtained through A. B. Verigo's aero-ionizer without any collateral factors. The patients inhaled negatively ionized air about 10^6 a second per 1 cm^3. The seances lasted a month, their duration gradually increasing to 10-20-30 minutes. In two cases out of eight no improvement was recorded. In two cases only a partial effect was obtained manifest in the apparently relieved respiration during the aero-ionization seance and for several hours afterwards, as well as in the abatement of night attacks; this made it possible to stop the almost daily injection of adrenaline. In the four remaining cases the results were excellent; the general condition of the patients improved, the attacks disappeared, and they regained their capacity for work.

We have applied aero-ionization with a negative charge for the treatment of bronchial asthma patients for 16 years.

We anticipated that it would first of all manifest itself in cases of lung and respiratory tract diseases, since it is only through the respiratory apparatus that aero-ions exercise their influence on the body.

Light negatively charged aero-ions were also obtained through A. B. Verigo's radium unipolar aero-ionizer of continuous action (A. B. Verigo and V. A. Paderni).

The negatively charged aero-ions were dosed with due consideration for the respiratory capacity and the number of aero-ions in 1 ml. of the air inhaled (at a distance of 5-10 cm. from the aero-ionizer tank of 2^{10} of light negatively charged aero-ions).

With the volume of inhaled air amounting to 400-500 ml. the patient received an average of 800 million light negatively charged aero-ions with every inhalation, and with the number of inhalations reaching 14-18 a minute, the quantity of aero-ions introduced into the lungs increased to 15 thousand million.

The seance lasted from 5 to 10 minutes; consequently, the patient received from 100 to 150 thousand million light negatively charged aero-ions at every seance. The course of treatment consisted of 10-30 seances.

Two or three courses of treatment with intervals ranging from 20 to 30 days are generally required to ensure a stable and lasting cessation of attacks.

Our observations show that the best therapeutical effect is obtained when a dose of 100-150 thousand million light negatively charged aero-ions is applied. Throughout the course of treatment the patient received the same quantity of aero-ions, larger doses were used only in cases of exacerbation of the disease.

By applying aero-ions we not infrequently succeeded in checking the attacks of asthma. In such cases the patient received, as a rule, from 50 to 100 thousand million aero-ions every 5-10 minutes, i.e., a total of 400-500 thousand million aero-ions in the course of the seance.

We had a total of 600 bronchial asthma patients (200 men and 400 women). Divided into age groups they comprised the following: 10 or under—2 per cent, from 11 to 20—8, from 21 to 30—22, from 31 to 40—33, from 41 to 50—20, from 51 to 60—13, 61 years or over—2 per cent. Twenty per cent of the patients had their first attack of bronchial asthma at the age of 10 or under, 20 per cent at the age of 11-20, 20 at the age of 21-30, 21 at the age of 31-40, 15 at the age of 41-50 and 4 per cent at the age of 51 and over.

Duration of the bronchial asthma disease: 20 per cent of the patients had suffered from bronchial asthma from several weeks to 5 years, 30 per cent from 6 to 10 years and 50 per cent 11 years and over.

The number of causes that brought about attacks of bronchial asthma in patients varied considerably.

In 8 per cent there was, as a rule, but one cause, namely, infection of the respiratory tract. In 21 per cent the attacks were brought about by odours, meteorological conditions and other causes. In 25 per cent the most frequent causes were negative or positive emotions combined with other factors, mentioned above. In 46 per cent neither the patient nor the physician handling the case could account for the attack.

An examination of the vegetative part of the central nervous system revealed that the attacks had originated in connection with the higher tone of the parasympathetic part of the vegetative nervous system. These patients also had attacks from various other, previously mentioned causes.

We recorded the physiological and therapeutic effect of the light negatively charged aero-ions by means of a number of clinical and laboratory examinations of our patients: we studied the changes in the blood, urine, faeces and sputum, instituted roentgenoscopy and roentgenography of the lungs and the heart, recorded the vital capacity of the lungs, and determined the resistance of blood serum colloids to the coagulator—sulphuric aluminium.

During the seance (therapeutic dose) the pulse rate dropped by 10-20 beats a minute, and the number of inhalations by 3-5 a minute. There appeared somnolency, yawning, a slight general weakness, and the need of rest.

Slower sedimentation of erythrocytes was registered, as well as a change in the character of the curve demonstrating the E.S.R. every 15 minutes. On the other hand, as shown by the curves, the pulse and inspiration rates increased with the application of larger doses, exceeding therapeutic ones; the patients complained of palpitation and dyspnea; there appeared excitation, insomnia, indisposition and weakness.

At the same time accelerated sedimentation of erythrocytes was apparent as well as a change in the character of the curve showing the E.S.R. every 15 minutes. During the course of treatment subjective improved work of the heart was observed in 82 per cent of the patients—the intermissions, palpitation and dyspnea disappeared. The pulse rate decreased by 10-15 beats a minute.

The emphasis on the second tone of the lung artery became less pronounced. The blood pressure dropped 5-12 mm. in cases when it was high, and, on the contrary, rose to normal when it was low.

Respiration became less frequent and approximated the normal type; the lung edges became more mobile; the amount of dry and moist crepitation diminished; in 90 per cent of the patients the secretion of sputum decreased; the vital capacity of the lungs increased by 500-600 ml.

Improved appetite and regular stool were recorded.

The daily quantity of urine increased by 200-700 ml. The general condition improved, in 60 per cent of the cases fatigue diminished and in 90 per cent sound sleep was registered.

In quite a number of cases roentgenoscopy of the thorax revealed an improved functioning of the diaphragm and respiration of the lung edges, and the disappearance or

diminution of stagnant phenomena in the lung hili. The dilated heart was reduced to normal dimensions.

The number of erythrocytes dicreased somewhat after the course of treatment but still remained within the limits usual for patients affected with this disease. This phenomenon is evidently due to the improved ventilation of the lungs. The Hb content did not change perceptibly.

The number of leucocytes which had increased at the beginning of treatment dropped to the average norm. The number of eosinophils increased during exacerbations, which generally set in between the 10th and 15th seances; towards the end of the course of treatment their number declined to the upper limit of the norm (in 80 per cent of the patients).

Eosinophilia was less pronounced in patients with infected respiratory organs than during remission. In cases when the number of the eosinophils was below the average, it assumed normal figures after treatment. The number of neutrophils reached after treatment the average norm; the number of lymphocytes increased to 40 per cent, declining after treatment to about 32 per cent.

No perceptible change was observed in the number of basophils and monocytes. The previously accelerated E.S.R. became slower, while the retarded rate was, on the contrary, accelerated and reached the normal figures. In ninety per cent of the patients affected with acute or chronic infection the sedimentation rate dropped to normal. Large doses of negatively charged aero-ions, exceeding two or three times the therapeutic doses, produced a reverse effect, accelerating in every case the sedimentation rate.

The resistance of blood serum colloids to sulphuric aluminium (Mátéfy test, modified by Bryulova and described by Landa Glaz) increased under the influence of a therapeutic dose of light negatively charged aero-ions.

Large doses, on the contrary, reduced the resistance of serum colloids. During treatment, the general condition of the patients, as a rule, deteriorated in between the 10th

and 15th seances. They became more irritable, suffered from insomnia, the attacks were more severe and even an asthmatic state appeared.

This was observed in both hospital and dispensary conditions. In cases of this kind the quantity of sputum generally diminished or it disappeared altogether.

The exacerbation continued for several days and then gradually (during 5-8 days) passed; in some cases, however, the attack came to an abrupt end at the culminating point and was followed by a satisfactory general condition.

During the periods of exacerbation in hospital, treatment was not stopped, whereas in dispensaries it was interrupted.

In 50 per cent of the patients the remission was lasting, in 39.5 per cent the attacks were weaker and less frequent, and only in the case of 10.5 per cent was the treatment of no avail.

An analysis of the results of treatment of patients with infection of the respiratory organs and during remission shows that the best results were obtained with patients who did not suffer from any infection.

The lesser effect obtained in patients with infection was due to the infection foci which continuously sustained the sensibilization of the body.

The method of aero-ionization (treating with light negatively charged aero-ions), in the case of bronchial asthma, produces either good or satisfactory results, especially when compared with other methods.

The important thing is that the body does not become accustomed to aero-ionization, quite the reverse, it becomes more and more sensitive to it.

The data available from various publications, as well as our own findings, show that the mechanism of action of the negatively or positively charged aero-ions should be viewed from the standpoint of the reflex theory. On the basis of a long and comprehensive study of the problem L. L. Vasilyev and his associates believe that "the aero-ions affect the functional state of the organs, notably the

skeletal muscles, partly in a reflex way, by stimulating the endings of the lung centripetal fibres which pass within the vagus nerves, and partly humorally, by changing the electrochemical properties of the blood flowing through the capillaries of the alveoli. This in turn affects, first of all, the functional state of the central nervous system, and, through it, directly the peripheral organs. Hence the electrohumoral mechanism of action of aero-ions on the organism is by no means isolated or autonomous. On the contrary, it is but a link inserted into the chain of more general and multi-form mechanisms of a neuroreflex character."

The negatively charged aero-ions have a similar effect on patients with bronchial asthma through the interoceptors ending in the mucous membrane of the trachea and bronchi. The impulses enter the nuclei of the vagus nerves, the thalamus and the cerebral cortex—directly into the dominant foci of heightened excitability, thereby immediately influencing the dominant. They cause a number of changes with a subsequent normalization of the functions of the central nervous system, which is related to the eventual fading of the dominant foci of heightened excitability. The clinical data lead to the conclusion that the negatively charged aero-ions have a desensitizing effect on patients suffering from bronchial asthma.

Consequently, the method of treatment with light negatively charged aero-ions, produced by the Verigo method, can be recommended for the treatment of bronchial asthma.

When no infection was evident, we treated the patients with conventional drugs, such as aspirin, pyramidon, phenacetin and other pharmacological preparations. In 219 cases bronchial asthma was treated with aspirin in doses of 1.0 gm. or aspirin (1.0 gm.) with caffeine sodio-benzoate (0.1 gm.).

To prevent bronchial asthma attacks in the period of premonitories or at the beginning of attacks, the patients were given aspirin with or without caffeine. In the case of over 50 per cent of the patients the method proved suc-

cessful—attacks were either checked or prevented. We recommended that patients retiring for the night should take aspirin (1.0 gm.) with ephedrin (0.05 gm.), or aspirin (1.0 gm.) with caffeine (0.1 gm.) and ephedrin (0.05 gm.) as a preventive. The result was that 60 per cent of the patients were not troubled with attacks at night. With the view to desensitizing the organism, we gave patients in a state of remission a dose of 1.0 gm. of aspirin every 5 or 6 hours for 6 to 8 weeks, the daily amount being 4.0-5.0 gm. The attacks ceased, reappearing only after a fresh outbreak of infection of the respiratory tract. Five of these 219 patients displayed heightened sensitivity to aspirin. A dose of 1.0 gm. of aspirin caused bronchial asthma attacks which developed into an asthmatic state. Aspirin with caffeine had no effect on 19 patients with an infection of the respiratory organs, and the attacks of bronchial asthma continued.

We presume that aspirin has not been used on any extensive scale in the treatment of bronchial asthma because it was administered in small doses—from 0.3 gm. to 0.5 gm. —which had no therapeutic effect on the patients.

The mechanism of action of aspirin consists in its desensitizing influence on the body. Aspirin acts through the cerebral cortex.

Pyramidon in doses of 0.5 gm., or a 0.5 gm. dose of phenacetin, or a 0.5 gm. dose of analgin in combination with 0.1 gm. of caffeine acts in the same way as aspirin. They can be used as preventives against bronchial asthma attacks. Pyramidon, phenacetin and analgin should be prescribed 3 or 4 times a day as a course of treatment lasting from 5 to 6 weeks. They have a desensitizing effect and may be successfully used both for prevention of attacks and as a means of checking their progress when they have appeared.

The action of these pharmacological drugs can be intensified by a simultaneous administration of 0.1 gm. of caffeine sodio-benzoate or of 0.025-0.05 gm. of ephedrin.

We think these preparations have a normalizing effect on the higher nervous activity.

The treatment of patients suffering from bronchial asthma with calcium chloride began in 1912. It was prescribed by Dr. M. Y. Aryev, Dr. V. A. Voinov and others, and was administered internally in 10 per cent solutions from 4 to 5 gm. a day, and intravenously in doses of 10.0 ml. of the same solution by the drop method, etc.; however, no marked results were obtained.

450 patients had previously been treated with calcium chloride administered internally and injected in 10 per cent solutions. In 50 per cent of the patients an improvement was recorded; the condition of the other patients remained unchanged.

Calcium chloride solutions should be recommended only when there is a profuse secretion of the mucous glands of the bronchi accompanied by pronounced spastic phenomena.

The mechanism of action of calcium chloride on bronchial asthma patients has not yet been investigated. We presume, however, that the pharmacological action is implemented through the central nervous system.

By the character of its effect calcium chloride falls under the heading of the desensitizing therapy.

5. TREATMENT WITH EMBYCHINE

In 1952-1953 R. G. Berger and I treated 21 bronchial asthma patients with embychine. We have not seen any reports in Soviet publications dealing with embychine treatment of bronchial asthma patients; reports from abroad say that Hurst (in 1943) treated bronchial asthma with nitrogen mustard and obtained favourable results in 80 per cent of the patients. Arjona (1944) also applied nitrogen mustard to 30 bronchial asthma patients and obtained results after the first two injections; in some cases the attacks ceased and did not recur for six months.

In the Soviet Union embychine was first synthesized by Professor V. G. Nemets at the Leningrad Technological Institute in 1933.

Embychine is biologically active and, according to some investigators, principally affects the nucleo-protein metabolism. And since the synthesis of nucleo-proteins is particularly intensive in the haemopoietic organs and the mucous membrane of the intestines, it is only natural that the greatest changes should occur precisely in these organs.

Embychine appears to act on the haemopoietic organs through the central nervous system: at first it causes somnolence and adynamia in, and reduces the reactivity of, most of the patients, then, in the course of treatment, it intensifies the reactivity of the body as a whole.

Embychine is manufactured in a dry state in doses of 10 mg. and in ampules of 10 ml. each. Before being administered, embychine is dissolved in 10 ml. of sterile saline or Ringer's solution. This done, the solution is drawn into a syringe, the amount depending on the quantity of embychine that is to be administered to the patient. The solution should be of a weak concentration; therefore saline solution is added into the syringe to make up a total of 20 ml. and injected intravenously. The injection of the embychine solution is immediately followed by an injection of 15-20 ml. of sterile saline or preferably Ringer's solution. This should be done without removing the needle from the vein. The additional injection of the solution reduces any local irritation of the wall of the vein and prevents phlebitis. Particular care should be taken that no liquid gets into the subcutaneous cellular tissue, on the skin or mucous membranes. Should a drop of the solution penetrate under the skin, a few ml. of saline or Ringer's solution must be injected in the site. If the solution got on the skin or the mucous, embychine should be washed off with water.

As shown by our observations, the methods of treatment play a major role and require great attention and persistence.

The experience of our clinic in studying treatment with embychine of patients suffering from leucosis or lymphogranulomatosis has enabled us to elaborate methods of treating bronchial asthma with due account of the individual requirements of each case.

In deciding on the dose to be used for the treatment of bronchial asthma, we considered the patient's normal haemopoiesis, his capacity for regeneration, the severity of the pathogenic process and the patient's individual sensitivity.

We administered embychine in doses ranging from 2 to 5 mg. The pharmacological dose was fixed in the process of treatment on the basis of clinical observations.

Embychine injections were made every other day or every third and sometimes every fourth day, depending on the patient's condition.

Before every injection the number of leucocytes was invariably determined as well as the differential blood count. A clinical blood analysis was made every 5 days.

These investigations helped, in each instance, to determine the dose and frequency of the embychine injections.

The results of treatment were judged by the effect obtained, i.e., by the cessation of bronchial asthma attacks, by the whole of the clinical course and by the degree of depression of lymphopoiesis and the corresponding change in the differential blood count.

We had 21 bronchial asthma patients under examination (18 women and 3 men). In 20 cases the first attack of bronchial asthma was preceded by an infection of the respiratory tract, and in one case by a psychic trauma. All the patients were severely affected and suffered from complications, such as chronic vesicular emphysema of the lungs, cardiac myofibrosis attended with phenomena of heart and lung insufficiency.

The patients belonged to various age groups, from 19 to 65. In 10 cases the duration of the disease ranged from 6 to 23 years and in 11 from 3 to 6 years. Twelve patients

were admitted to the clinic in a very bad state: they had 6-7 and more attacks a day.

Embychine was administered in various doses. The number of injections varied from 4 to 10, and the quantity of embychine injected, expressed in mg., ranged from 19 to 51.5 throughout the course of treatment.

In 8 cases a definitely pronounced effect was obtained after the first injection—the attacks were checked. In 3 cases the attacks ceased after the second injection, and in 3 cases after the third. In 5 cases the number of attacks decreased after the first injection from four or five a day to one or two. In six patients a general improvement was obtained. The patients came out of the asthmatic state; the number of attacks remained the same, but from the first day of treatment they were checked with adrenaline, ephedrin and theophedrin.

In three cases the general condition improved but the attacks continued; the condition of two patients deteriorated, the number of daily attacks increased from one or two to seven, following which embychine treatment was stopped.

If the attacks recurred a week or two after the course of treatment, we again prescribed 1 or 2 injections, and the attacks ceased once more.

It should be noted that embychine had the least effect on patients whose disease was of long duration.

The cases given below will serve as illustration.

Patient E. G., female, aged 32 (case No. 20069), entered the therapeutic clinic of the faculty on December 24, 1951. Was transferred to the hospital therapeutic clinic on April 29, 1952, and discharged on May 29, 1952. Diagnosis: bronchial asthma, chronic asthmatic bronchitis and chronic vesicular emphysema of the lungs. On examination myodystrophy of the heart, and cardiac and respiratory insufficiency of the II or III degree were found.

Anamnesis included measles, scarlet fever, whooping cough, relapsing pneumonia and, in addition, a number of psychic traumas.

The patient was admitted to the therapeutic clinic of the faculty in a severe asthmatic state which lasted 5 months. The number of attacks varied daily from 5 to 7. The patient was given the following therapy: 16 injections of aloe, 120.0 of PAS, 14 seances of aero-ionization with

a negative charge, 20 injections of a 5 per cent solution of sodium salycilate, a course of treatmcnt with dibasol, a course of treatment with intravenous injections of nicotinic acid, and tissue grafting of the adrenal gland according to the method introduced by Rumyantsev.

No effect was, however, obtained, and the attacks continued.

To check the attacks the patient received daily adrenaline injections per 1 mg. 6 or 7 times a day.

Following the transfer to the hospital therapeutic clinic the patient received during the period of April 29-May 16 one tablet of theophedrin three times a day and a 0.25 per cent solution of novocaine intravenously (according to schedule cited on p. 34).

By May 16 the attacks declined to 4 or 6 a day, and her condition improved.

On May 16 therapeutic treatment was discontinued and embychine prescribed. After the first two injections of embychine (6 mg. per injection) the patient began to sleep both during the day and night; after the third injection the number of attacks dropped to one a day, and the patient continued to sleep both by day and by night. After the fourth injection the attacks ceased, and the asthmatic state disappeared. All told, 6 injections were made and 34 mg. of embychine administered. The patient bore well the injections, and there were no complications. On May 29 the patient was discharged in a good condition. The remission lasted a month, after which the patient caught cold, and attacks set in again; these were quickly checked by means of adrenaline (after injecting 1 mg.).

The patient was not subjected to any prolonged asthmatic state as observed in the clinic.

Patient E. A., female, aged 29 (case No. 13607), was admitted to the hospital therapeutic clinic on October 10, 1951, and discharged on December 6. Diagnosis: bronchial asthma, chronic bronchitis, chronic vesicular emphysema of the lungs and myodystrophy of the heart. Respiratory insufficiency of the I or II degree was recorded.

Chronic bronchitis was of eight years' duration. The disease was due in a measure to her unhealthy occupation.

The first asthmatic paroxysm which had occurred 4 years before was connected with previous cooling. At first the attacks were rare, but then they became more frequent and began to appear after an exacerbated catarrh of the respiratory tract and cooling.

In the summer of 1951, when the patient was pregnant, her condition sharply deteriorated. A minor Ceasarean section was performed which still more aggravated her condition. On August 20 the patient was taken to the Uritsky hospital in a bad state, where she remained until October 10.

In hospital the patient suffered from a severe continued asthmatic state, aggravated by 6 or 7 bronchial asthma attacks a day.

The attacks were checked for a few hours with injections of 1 mg. of adrenaline and then an asthmatic state set in again. In the Uritsky hospital the patient received a course of treatment consisting of intramuscular penicillin injections, a novocaine block and a course of intravenous injections of 10 per cent calcium chloride in doses of 10.0 ml. a day, as well as other therapeutic treatment.

The patient was transferred to the hospital therapeutic clinic in an acute asthmatic state where from October 10 to October 25 she received a course of penicillin treatment—30,000,000 I. U.—and a course of novocaine treatment. Novocaine was injected intravenously, and a bilateral vago-sympathetic block was administered according to A. V. Vishnevsky's method, which relieved the patient for two hours—checking the attack, but then her condition again seriously deteriorated.

A dose of 2 mg. embychine was injected when the patient was in a severe asthmatic state. The same quantity was injected three days later. After the second injection the patient's condition markedly improved, the attacks became less frequent, and the asthmatic state disappeared. The patient received 7 embychine injections totalling 19 mg. The first four injections were made with intervals of 1-4 days, and the following with breaks of 6-9 days. The patient was discharged in December 1951 in a satisfactory condition. No asphyxial paroxysms were recorded during the two weeks that followed her discharge from hospital. But once the patient started working, exacerbated bronchitis was again recorded and attacks reappeared, from one to five a day.

During the year the patient was given sick leave 5 times. As seen from the above, the influence of environment on the course of attacks was apparent, so we raised the question of the patient changing her occupation.

Patient A. I., female, aged 36 (case No. 17483), was admitted to the hospital therapeutic clinic on November 14, 1951. Diagnosis: bronchial asthma and residual pneumonia phenomena.

The patient had been ill with bronchial asthma for three months. After the first injection of 4 mg. of embychine the number of attacks diminished from five to one and after the second injection they ceased altogether. All in all, five injections of embychine were made. On December 6, 1951, the patient was discharged.

There were no bronchial asthma attacks in the following year.

Patient A. A., female, aged 49 (case No. 8089), was admitted to the hospital therapeutic clinic on May 9, 1952. Diagnosis: bronchial asthma (without infection foci). The patient had been affected with bronchial asthma since 1949. Treatment with embychine was begun after other kinds of therapeutic treatment had failed to produce any effect. The patient was detained in hospital for 28 days. On June 7, 4 mg. of embychine were injected intravenously. All told, five injec-

tions were made, totalling 20.0 mg. The attacks ceased, and the patient was discharged on June 21 in a good condition.

It should be noted that no favourable results were obtained when bronchial asthma patients with infection foci (bronchiectatic disease and chronic non-specific pneumonia) were treated with embychine; the reverse occurred—an exacerbated asthmatic state and more frequent bronchial asthma attacks were recorded.

Other phenomena observed in the treatment of bronchial asthma with embychine are given below.

No collateral effects were recorded in 4 cases after injection of embychine. In 17 cases nausea and predisposition to vomiting were observed; 5 patients complained of dizziness and loss of appetite ond 2 of dryness in the nose and nasopharynx three or four hours after injection of embychine. One patient had watery evacuation of the bowels for two days and one suffered from sialorrhea. However, these collateral effects passed in the course of the day, and the next day the patients felt well. We used anaesthesin and aeron as drugs, and in some cases administered injections of a 1.0 mg. solution of sulphuric acid atropine.

It is worth noting that no leucopenia was observed in patients suffering from bronchial asthma; it appeared when the patients were treated for lymphogranulomatosis. The number of leucocytes did not drop below 3,000, and in 6 cases did not change either before or after treatment. In most cases the number of lymphocytes diminished as a result of an increase in the number of neutrophils.

Lymphopenia and changes in the clinical picture often served as indications for stopping or continuing embychine injections. The point should be stressed that our patients showed an increased number of leucocytes and lymphocytes 3 or 5 days after the injection—an indication that treatment should have continued.

During treatment a reduced number of erythrocytes and a lower haemoglobin content was recorded, the former diminishing by 500,000-700,000 and the latter by 6-8 per

cent. After treatment they reached initial figures. The number of reticulocytes and thrombocytes remained unchanged.

In most cases the E.S.R. returned to normal during treatment. When the figures were normal, the E.S.R. remained unchanged. During treatment the arterial blood pressure was normal in 18 cases, while in 3 cases it dropped by 10 to 15 mm. Hg at the expense of the maximal pressure.

No deviations from the average norm were observed in the urine of bronchial asthma patients when treated with embychine, with the exception of those who had been in a protracted asthmatic state during the period of complications. An examination of these patients revealed traces of protein and the presence of 10 to 15 leached erythrocytes in the sediment within the field of vision. When treatment with embychine was completed, the protein and erythrocytes in the urine disappeared.

In five cases eosinophils were found in the sputum before treatment, and after treatment.

The above leads to the conclusion that embychine is an effective means of treating bronchial asthma, particularly when the patients are not affected with chronic infection foci.

No final conclusion can as yet be made about the mechanism of action of embychine, but we can say that it acts through the vascular receptors on the central nervous system—the cerebral cortex, the dominant foci of heightened excitability and then on the lungs.

6. TREATMENT BY MEANS OF V. P. FILATOV'S METHOD OF TISSUE GRAFTING

Tissue therapy has been widely applied in the treatment of bronchial asthma. Priority in elaborating the method belongs to Academician V. P. Filatov, Stalin Prize winner, who explained the effect of grafted tissues by the presence in the conserved tissue of so-called biogenic stimulators—

substances which activate the vital processes but the chemical composition of which is not known.

Certain modifications in this method were introduced by Dr. G. E. Rumyantsev, who suggested that conserved tissue taken from young healthy animals be used for grafting. To date a number of innovations have been introduced in V. P. Filatov's and G. E. Rumyantsev's methods in respect to the timing of subsequent graftings, the selection of tissues for grafting, the preparation of the tissues, the method of grafting, etc.

In the early stage of treating bronchial asthma, no indications or contraindications were worked out for the application of this kind of therapy; neither were the objective data suggested by which the effectiveness of the treatment could be judged. A serious shortcoming worth mentioning is the absence of a scientifically substantiated explanation regarding the mechanism of action of the transplantation agent, as well as the absence of any definite standards to follow when preparing the materials for grafting. Unfortunately, these problems have not as yet been resolved.

We applied V. P. Filatov's method of grafting in treating 112 patients suffering from bronchial asthma. We treated 62 patients by grafting adrenal gland tissue, 30 patients by grafting placenta tissue, and 20 patients by grafting simultaneously adrenal gland and placenta tissues. From 2 to 4 transplantations were applied to each patient with intervals ranging from 30 to 40 days. In the case of 54 patients tissue grafting was applied during an aggravation of bronchial asthma and when repeated attacks occurred daily, and in the case of 58 patients—during a remission. In 21 cases out of 54 the attacks ceased within periods ranging from 2 weeks to 3 months. The general condition, sleep and capacity for work improved, and the excretion of sputum sharply declined. The attacks reappeared as a result of an aggravated infection of the respiratory tract and bronchi. In 18 cases the attacks continued, but less frequently; they became of shorter duration and were quickly checked with

injections of 1 mg. of adrenaline. In 15 cases the general condition deteriorated; the attacks became more intense and of greater duration. Injections of 1 mg. of adrenaline failed to check asphyxial paroxysms. These patients had a sharply pronounced chronic vesicular emphysema of the lungs and myofibrosis of the heart attended with phenomena of cardiovascular and respiratory insufficiency of the I or II degree; in addition, 12 patients were affected with chronic non-specific pneumonia.

Of 58 patients in a state of remission, 8 showed an exacerbation of the asthmatic state after the grafting of adrenal gland or placenta tissues. Attacks of bronchial asthma appeared, accompanied by exacerbated chronic non-specific pneumonia. The condition of the other patients improved.

We conceive the mechanism of action of the transplant from Pavlov's standpoint. Here is what I. P. Pavlov says with regard to the mechanism of action on the body of substances that are introduced into it: "When a substance is introduced into the organism and a number of deviations from norm ensue it would be wrong to view these deviations as the direct effects of the introduced substance on various organs. It may well be—and it is a fact—that only some changes in normal functions are actually a direct result of the influence exerted on an organ by the substance, while many others are no more than indirect consequences due to the close interconnection of the organs in the organism where the change in one function necessarily involves changes in others."

The transplant, introduced into the body by means of surgical intervention, becomes a non-adequate physical or chemical stimulant for the body and the tissues surrounding it, which acts on the local receptors of the connective tissue of the skin and subsequently by way of reflex, through the spinal cord, on the central nervous system. In addition, the transplant also acts humorally, the components of the transplant penetrating into the blood.

The new focus that has arisen in the periphery in the site of the introduction of the transplant is bound to exercise a corresponding influence on the central nervous system, and notably on the dominant foci of heightened excitability of bronchial asthma patients. The responsive reaction of the body appears to depend on the condition of the central nervous system and the dominant foci of heightened excitability.

In some cases the dominant foci of heightened excitability are sustained by stimulations from the periphery and in others they, on the contrary, fade away. Hence, in some cases the attacks of bronchial asthma clinically cease, while in others they, on the contrary, become aggravated.

These processes appear to occur in the central nervous system according to the laws of parabiosis.

Our data lead to the following conclusions. In some cases tissue therapy may prove to be an effective curative method. The transplant introduced into the body changes the reactivity of the body as a whole and, notably, of the pulmonary-respiratory apparatus.

Treatment by means of V. P. Filatov's method of grafting should be administered with due consideration for the individual peculiarities of the patient's body affected with bronchial asthma. Further investigation of this problem is required to specify the indications for applying this method of treatment on patients suffering from bronchial asthma.

7. TREATMENT WITH CAFFEINE AND BROMIDES

We treated bronchial asthma patients with conventional doses of caffeine and its salts in cases when, under the influence of prolonged and severe attacks of bronchial asthma, or because of complications (chronic vesicular emphysema of the lungs of myofibrosis of the heart), acute insufficiency of the right ventricle set in, most frequently attended with pulmonary-respiratory insufficiency. The patients received caffeine sodio-benzoate in doses of

0.1-0.2 gm. twice or three times a day, that is from 0.3 to 0.6 gm. a day, or subcutaneous injections of a 20 per cent caffeine sodio-benzoate in doses of 0.2-0.3 gm., totalling from 0.4 to 0.9 gm. a day.

When prescribing larger doses of caffeine we proceeded from the fact that caffeine, by acting on the central nervous system, promotes the working capacity of the myocardium, stimulates the vascular centre and intensifies coronary blood circulation, increasing at the same time the gas exchange attended with a simultaneous greater formation of carbon dioxide. The advantage of caffeine lies in its rapid action and its shortcoming in the rapid fading of its effect.

To intensify and prolong the action of caffeine during attacks, we administered it in combination with aspirin (0.1 gm. of caffeine sodio-benzoate and 1.0 gm. of aspirin) or pyramidon (0.5 gm.) or phenacetin (0.5 gm.) with the same doses of caffeine sodio-benzoate.

Our observations showed that the combined administration of caffeine with aspirin or pyramidon, or phenacetin in combination with 0.05 gm. of ephedrin intensified the action of caffeine, checking the attacks in more than 30 per cent of the patients. It is worth noting that when 1 mg. of adrenaline proved of no avail, the simultaneous subcutaneous injection of 0.2 gm. of caffeine greatly increased the effectiveness of adrenaline, and the attack was checked. We obtained similar results when administering simultaneous subcutaneous injections of 0.05 gm. of ephedrin and 0.2 gm. of caffeine.

The action of caffeine on the cerebral cortex was studied by A. A. Lindberg in 1935. According to his data, caffeine brings about heightened excitability of the nervous cells, without intensifying the processes of excitation in the cortex. The results obtained by A. A. Lindberg show that large doses of caffeine cause rapid weakening and exhaustion of the nerve elements.

Our observations, however, show that when administered subcutaneously during an attack or asthmatic state, or

when phenomena of insufficiency of the right ventricle and the lungs are apparent, caffeine causes excitation of the central nervous system—the cerebral cortex, the respiratory and vasomotor centres and the centre of the vagus located in the medulla. This results in a dilatation of the peripheral vessels of the skin, of the muscular apparatus, and of the brain, coronary and renal vessels; respiration becomes deep, increasing simultaneously the consumption of oxygen and the removal of carbon dioxide from the lungs.

The blood is redistributed in the body, pulmonary circulation is relieved, and the blood supply of the heart and its work improved.

We treated 120 bronchial asthma patients with small doses of caffeine from 0.001-0.003 to 0.1-0.2 gm. administered internally three times a day in combination with sodium bromide in small doses from 0.001-0.005 to 0.2-0.3 gm. At the same time we applied anti-bacterial therapy. We tried to dose caffeine and sodium bromide in accordance with the type of higher nervous activity. I. P. Pavlov wrote: "... the weaker the type of nervous system and the given nervous state, the smaller must be the dose of bromides."

Guided by experimental data obtained in laboratory investigations, I. P. Pavlov warns physicians against using large doses of bromides: "If you administer an excessively large dose, you may obtain an injurious instead of a beneficial effect; you may cause the patient serious injury."

If bromides, applied in small doses, restore and intensify the inhibition process, their excessive use, on the contrary, weakens the processes of internal active inhibition and leads to phenomena of deconcentration and disinhibition.

The works of I. P. Pavlov and his associates show that caffeine intensifies the process of stimulation and through the mechanism of negative induction promotes the restorative processes of internal inhibition; in other words, caffeine acts on the process of stimulation in the same way as bromides act on inhibition.

Hence, simultaneous treatment with a combination of bromides and caffeine (bromides, intensifying the inhibition process, and caffeine related to the excitation process) merits particular attention. I. P. Pavlov viewed the influence of these two preparations as two levers. These levers can restore the disturbed relationship between the processes of stimulation and inhibition. In the case of bronchial asthma patients small doses of bromide and caffeine exerted a normalizing influence on the central nervous system. The dominant foci of heightened excitability gradually faded away, with attacks of bronchial asthma disappearing simultaneously.

Going by clinical data, good results were obtained in 98 cases as a result of treatment with combined therapy, i.e., with sodium bromide and caffeine in doses depending on the type of higher nervous activity: sleep became normal and an appetite appeared, while dyspnea, accompanied by palpitation, weakness and headache disappeared. The course of treatment lasted from three weeks to two months. The bronchial asthma attacks were less pronounced than in patients who did not receive this kind of treatment. All the patients thus treated were able to return to their occupations.

8. OTHER KINDS OF THERAPY

This section is devoted to symptomatic and other kinds of therapy largely aimed at treating complications attending bronchial asthma.

We treated 87 of our patients for 15 days with intravenous injections of a 40 per cent solution of glucose in daily doses of 10.0-20.0 ml. The same therapy had been applied to 31 patients before they entered the clinic.

The indications for injecting glucose are based on the fact that, in contradistinction to the skeletal muscle, the myocardium steadily preserves a high level of carbo-hydrates, and particularly of glycogen even under conditions

when the amount of glycogen in the skeletal muscle sharply diminishes, as for instance in the case of physical work, injections of adrenaline, etc. On the other hand, the glycogen content in the myocardium drops only when anoxemia of the myocardium develops as a result of its lowered blood circulation.

The administration of glucose solutions to asthmatics is indicated in the period of complication by chronic vesicular emphysema, cardiac myofibrosis, insufficiency of the right ventricle, and particularly when toxic and infection foci are present in the body. Another point to be borne in mind is that the quantity of sugar in the blood serum of asthmatics is somewhat lowered.

During the course of treatment the patients' general condition improved, but the attacks went on unabated. Fewer attacks were observed in patients undergoing a toxic and infection period.

Hence patients suffering from bronchial asthma should be treated with glucose mainly when the following indications exist: infection foci in the lungs and insufficiency of the right ventricle.

Forty-eight patients with complications in the shape of chronic vesicular emphysema of the lungs and myofibrosis of the heart, accompanied by phenomena of insufficiency of the right ventricle and the lungs were treated with diuretin, administered three times a day in doses of 1.0 gm. A prolonged administration of the drug in the form of a 2-4 weeks' course of treatment proved effective.

In most cases, diuretin (1.0 gm.) combined with ephedrin (0.05 gm.) prevented bronchial asthma attacks and even checked those that had already appeared.

We treated 18 patients suffering from bronchial asthma with theobromine in doses of 0.5 gm. three times a day during three or four weeks and obtained good results; cardiac and lung insufficiency disappeared, but the attacks persisted.

Forty-one bronchial asthma patients were treated with

a 10 per cent solution of ascorbic acid in doses of 100-200 mg. From 15 to 25 injections were administered during the course of treatment.

Patients suffering from uncomplicated bronchial asthma showed good results: the attacks ceased and the general condition improved. No favourable results were obtained in patients affected with chronic vesicular emphysema of the lungs, but an improved general condition was recorded. The attacks persisted but they became less intense and pronounced.

In no case were bronchial asthma attacks stopped by 100-200 mg. injections of ascorbic acid, administered during attacks.

B. B. Kogan and G. P. Bogdanova summed up available data on treatment with ascorbic acid. They have ascertained that its daily quantity in the urine of bronchial asthma patients is lowered, particularly in the period of attacks.

They have also concluded that ascorbic acid undoubtedly has an anti-anaphylactic effect on bronchial asthma patients. It weakens the manifestation of anaphylactic reactions and lessens the change in protein balance characteristic of a hyperergic state.

Experimental data obtained on dogs by I. P. Kozhevaya, A. I. Kryzhanovskaya, E. S. London and F. I. Rivosh suggest that after intravenous injections of 200-400 mg. of ascorbic acid the secretion of adrenaline increases as much as five-fold at the end of the first hour.

In addition, we treated over 250 patients who had bronchial asthma accompanied by phenomena of polyhypovitaminosis. The latter was observed most often in patients suffering from acute or exacerbated chronic infection, complicating the course of bronchial asthma. The patients received 200-300 mg. of ascorbic acid, 25-30 mg. of thiamin and 30-50 mg. of nicotinic acid with 1.0 gm. of glucose two or three times a day. In addition 2 or 3 tablespoons of codliver oil or 10,000-20,000 I.U. of vitamin A a day were prescribed.

We considered the prescription of vitamins as being indicated particulary for patients suffering from bronchial asthma and affected with chronic non-specific pneumonia or chronic vesicular emphysema of the lungs. A marked reduction in the content of thiamin and of ascorbic and nicotinic acids in the urine was observed in every case, and particularly during a prolonged asthmatic state and severe course of bronchial asthma.

Within a month after receiving vitamins the general condition of the patients improved; they had a better appetite, were cheerful and physically fit.

Vitamin treatment favoured the normalization of the functions of the asthmatic's body and laid the foundations for recovery.

In 1950, I. Kairyukshtis published data on neobenzinole treatment of 31 bronchial asthma patients. His investigations showed that an intramuscular injection of 0.8 of neobenzinole sufficed to obtain a remission lasting several months. The mechanism of action of this preparation consists in that at first a local and then a general reaction appeared on the site of the injection, accompanied by leucocytosis.

In 1951-1953 we had 11 bronchial asthma patients under observation. Six had complications manifested by chronic vesicular emphysema of the lungs and myofibrosis of the heart, and five chronic non-specific pneumonia. After an injection of 0.8 of neobenzinole the first six patients showed a pronounced general reaction, followed in two cases by a remission lasting from 6 to 7 months, and in the four remaining cases from 2 to 3 months. Of the five patients with chronic non-specific pneumonia, two showed an improvement during the rise of temperature, after which the attacks assumed their usual course. The condition of the other three patients improved, but the attacks persisted.

We believe that the mechanism of action of this non-specific stimulant develops along the following lines. After neobenzinole is injected, rival dominant foci of heightened

excitability arise in the central nervous system simultaneously with the development of a local reaction, the foci being so intense as to extinguish the dominant foci of heightened excitability of bronchial asthma. This is manifested clinically by the checking of bronchial asthma attacks. On the other hand, when a local focus, arising out of a neobenzinole injection, fades away (the rival dominant focus) and is not sustained from outside, while the dominant focus of bronchial asthma reappears, we witness clinically an attack of bronchial asthma and a prolonged asthmatic state. It is difficult to say how effective this therapy is since we have insufficient experience on the subject.

CHAPTER III

THERAPEUTIC TREATMENT OF BRONCHIAL ASTHMA ATTACKS

Subcutaneous injections of adrenaline in 1:1000 solutions and in doses of 1 ml. have been applied in Russia for checking bronchial asthma attacks since 1911-1912. Subcutaneous injections of 1 ml. of adrenaline were indicated in cases of pronounced attacks of bronchial asthma.

Adrenaline thus injected acts on the central nervous system and the endings of the sympathetic nerves of the smooth muscles of the bronchi, which is followed by a relaxation of the muscles of the bronchi and lesser hyperemia, swelling and hypersecretion in the bronchioles. In addition, adrenaline stimulates the cardiac fibres of the sympathetic innervation of the heart and dilates the coronary vessels, thereby improving the blood supply of the heart; it also intensifies the contractions of the heart, accelerates its rhythm, heightens the vascular tone and increases the blood pressure. It should be borne in mind that when administered in ordinary doses, adrenaline has a stimulating effect on the respiratory centre and the parasympathetic part of the vegetative nervous system.

In the case of some patients 1 mg. of subcutaneous injection of adrenaline causes a tremor of the extremities, pallor of the skin integument and visible mucous membrane, headaches, palpitation, insomnia, etc.

When injected subcutaneously, 1 mg. of adrenaline soon removes the bronchial asthma attacks without causing any complications in the shape of chronic vesicular emphysema

of the lungs, chronic non-specific pneumonia, bronchopneumonia, etc. The attacks cease and may not recur for a long time. More frequently, however, the effect of adrenaline is confined to a few hours, and, as a rule, when bronchial asthma becomes exacerbated, the patient must be given from 6 to 10 mg. of adrenaline a day. In some cases from 30 to 36 mg. of adrenaline a day were given to patients suffering from bronchial asthma attacks complicated by bronchopneumonia, or during an exacerbation of chronic non-specific pneumonia.

Observations conducted by V. V. Fokina have shown that adrenaline quickly disappears from the blood and cannot prevent recurrent attacks.

The question as to the toxicity of adrenaline is still open to discussion. When injected subcutaneously, adrenaline does not decompose for a comparatively long time in the site of injection—in the muscles and lungs—and even in the blood.

"The fate of adrenaline injected into the body has not by any measure been clarified, though we are aware of the property of adrenaline to decompose readily," wrote Professor V. Nikolayev. "Adrenaline disintegrates little, but excessive adrenaline disappears from the blood very rapidly; the decomposition of adrenaline goes on vigorously in the capillary network, and the liver and the intestines are the chief site of its destruction."

When patients are treated during an attack, the question constantly arises whether large quantities of adrenaline may be injected without detriment to the body. Large quantities of adrenaline are often injected at the patient's request or by the patient himself.

When adrenaline is injected repeatedly, it is advisable to administer simultaneously pharmacological drugs which stimulate the respiratory centre. When such combined therapy is applied, adrenaline is more effective.

We are unaware of patients becoming accustomed to adrenaline.

Among the mixtures designed for subcutaneous injection, of which adrenaline forms a part, anti-asthmocrine (a preparation composed of a mixture of equal volumes of pituitrin showing an activity of 4 I. U. in 2 ml. and a 1:1000 solution of adrenaline) is worth noting. The indications for its application are the same as for adrenaline. We find that the effectiveness of this preparation does not exceed that of pure adrenaline when used in the same dose.

If within 10-15 minutes an injection of 1-2 mg. of adrenaline produced no results, adrenaline, in combination with sulphuric acid atropine and pantopone, was injected intravenously according to the following prescription: 1 mg. of each—adrenaline and sulphuric acid atropine, and 1 mg. of pantopone in 10.0 ml. of a 40 per cent solution of glucose in doses of 1.0 ml. of this mixture. (Small doses of pantopone have a stimulating effect.)

The mixture should be prepared *ex tempore* and introduced into the vein with due care and very slowly in doses of 1 ml. in the course of 10-15 minutes. When the first drops are injected, the patients show lesser contraction in the thorax and diminished asphyxia, though at the same time dyspnea increases, accompanied by headache, weakness, dizziness, etc.

When the mixture is injected intravenously, all these sensations manifest themselves more intensively than during a subcutaneous administration of adrenaline.

The collateral negative effect which results from the application of this drug is, however, slight, compared with its favourable effect.

Most patients feel better and in a few minutes fall asleep. In order to sustain the tone of the central nervous system and the sympathetic part of the vegetative nervous system, 1 ml. of these pharmacological drugs should be introduced once more an hour or two later, despite the fact that the patients, fearing the collateral negative phenomena which develop during their introduction, are not always willing to have these preparations administered repeatedly.

Adrenaline is applied locally, in the form of drops, when treating vasomotor rhinitis which often attends bronchial asthma. It is introduced in combination with a novocaine solution into the trachea and bronchi, producing good results. We used the following prescription: 50.0 ml. of a 0.25 per cent novocaine solution and 1 mg. of adrenaline.

When this was introduced during an attack, the latter ceased, and in some cases the remission lasted several hours or days. We may presume that the infusion of an adrenaline solution through the bronchi or lungs was more effective than other methods. We used a similar composition of a novocaine and adrenaline solution for injections when preparing the patients for bronchography.

Adrenaline is also used for inhalation in compounds with oily substances, such as "aspazan," for instance, as their base.

Adrenaline belongs to a group of substances possessing little stability, particularly in alkaline media. When combined with other chemical substances, it decomposes rather quickly. Hence, one should avoid mixing in a syringe adrenaline with other pharmacological drugs, such as caffeine solutions or camphor oil. In such a mixture adrenaline decomposes and does not produce the anticipated results. Such mixtures are inadmissible for the additional reason that adrenaline, by contracting the vessels, impedes the absorption of the pharmacological drugs injected concurrently with it.

When adrenaline is injected subcutaneously or intravenously, the central nervous system and the endings of the fibres of the sympathetic nerves become stimulated; it also has an effect on the respiratory centre and the centre of the parasympathetic part of the vegetative nervous system, which results in a change in the state of the dominant foci of heightened excitability. With the stimulation of the endings of the sympathetic fibres the transmission of impulses from the mucous membrane of the bronchi and lungs to the centres of the cerebral cortex apparently

changes and the dominant foci of heightened excitability fade away during the action of adrenaline. When adrenaline is applied locally on the mucous of the respiratory tract, and particularly when it is injected together with a novocaine solution, anaesthesia of the peripheral receptors of the bronchi takes place, the transmission of impulses from the peripheral interoceptors simultaneously ceases, and conditions are created for the dominant foci of heightened excitability to fade away. When adrenaline and novocaine cease acting on the central nervous system and the endings of the sympathetic nervous fibres, the reflex arc becomes restored: the lungs—the central nervous system—the lungs; the dominant foci of heightened excitability are revived, and at the same time an attack of bronchial asthma recurs.

Nearly all our patients used adrenaline in the above-mentioned therapeutical doses to check attacks, the results being satisfactory. If the injection was made at the beginning of the attack, the latter was checked quickly. We observed no complications in patients when administering adrenaline subcutaneously, intravenously or locally. Subcutaneous, intravenous or intratracheal infusions of adrenaline are a reliable method of checking an attack of bronchial asthma and of enabling the patient to calm down, fall asleep and regain his strength and capacity for work.

We treated over 90 per cent of our patients with hydrochloric acid ephedrin. Ephedrin has the same effect as adrenaline, but the former acts on the respiratory centre, stimulating it and effecting at the same time an intense and prolonged rise in the ventilation of the lungs when applied in therapeutical doses; toxic doses paralyze the respiratory centre (N. V. Vershinin).

Ephedrin is more stable than adrenaline and may be administered to the patient per os. In Russia ephedrin was used in folk medicine as far back as the beginning of the last century in the form of an infusion known as "Kuzmich's medicinal herb." In 1938, ephedrin was synthesized by the

Soviet pharmaceutical industry and widely used for the treatment of bronchial asthma and cardio-vascular diseases (B. B. Kogan and M. M. Grinberg, A. A. Melik-Adomyan, I. A. Levitin, S. F. Gottesfried and others). Hydrochloric acid ephedrin is available in tablets of 0.025 and 0.03 gm. and in ampules in 1 ml. doses of a 5 per cent solution. Our bronchial asthma patients received hydrochloric acid ephedrin during attacks and also as a preventive during remissions. For the latter purpose patients received 0.025-0.05 of hydrochloric acid ephedrin two or three times a day. Doses of 0.025 or 0.05 gm. of hydrochloric acid ephedrin were administered to check an appearing attack and to prevent night attacks.

Some patients received 0.05 gm. of hydrochloric acid ephedrin subcutaneously, the same indications serving as a guide.

Ephedrin was prescribed both in the period of exacerbated attacks of bronchial asthma and during remissions. Patients with bronchial asthma were given doses of 0.05 gm. every 8 hours, three times a day.

Ephedrin was administered in such dosages for two or three months.

To obtain a most rapid effect, we recommended that patients should not swallow the tablet or powder but keep it in the mouth cavity: in this way ephedrin penetrated into the blood directly through the mucous membrane. In some patients ephedrin caused a headache, tremor of the extremities, dizziness, weakness and insomnia. These collateral effects were, however, of little significance compared with the basic positive effect recorded when ephedrin was used for treatment.

In patients who did not suffer from any complications, the effect of hydrochloric acid ephedrin was felt within 5-15 minutes. In cases of complications, such as chronic vesicular emphysema of the lungs, etc., the effect of ephedrin was retarded: it began in 30-60 minutes after the administration of the dose.

Ephedrin produced no marked results in infection processes in the lungs or bronchi: in bronchopneumonia, aggravated bronchiectatic disease, etc.

The above shows that in cases of acute infections local inflammatory phenomena inhibit the transmission of impulses by the sympathetic fibres of the vegetative nervous system. Due to intoxication the excitability of the respiratory centre and the cerebral cortex is greatly reduced, the result being that the preparation, though highly effective in different conditions, becomes of little avail. In addition, patients receiving ephedrin for any length of time have periods when it ceases to exercise any influence. This is evidently due to overexcitation of the respiratory centre, which sets in as a result of a prolonged administration of large doses of ephedrin.

During such periods we stop treatment with ephedrin for three or four days and prescribe atropine to react on the parasympathetic part of the vegetative nervous system. After an interval of three or four days ephedrin has its usual pharmacological effect on the patients.

We must ascertain the most effective dosage for each and every case and apply it in conformity with individual indications. According to our observations, the effect of ephedrin in bronchial asthma patients lasts from 2 to 8 hours.

We have widely used ephedrin in combination with aspirin and caffeine as a means of preventing attacks and an asthmatic state in patients (0.05 of ephedrin, 0.05 of pure caffeine and 1.0 of aspirin) for the past ten years. We believe that the injection of these preparations has a complex effect on the central nervous system: under the influence of aspirin the excitability of the cerebral cortex becomes heightened; under the influence of caffeine the excitability of the nerve tissue is enhanced without the processes of excitation becoming heightened in the cerebral cortex; under the influence of ephedrin the excitability of the respiratory centre becomes greater.

As shown by our experiment, such a combination of ephedrin, aspirin and caffeine, when used in the above doses, produces good results and merits attention in cases when patients with bronchial asthma do not suffer from any infection foci in the respiratory organs and when the body is in a state of remission.

Soviet industry manufactures theophedrin, which is available in packages of 10 tablets, each consisting of 9 ingredients: 0.05 gm. of theophelin, 0.05 gm. of pure caffeine, 0.2 gm. of phenacetin, 0.02 gm. of luminal, 0.05 gm. of theobromine, 0.2 gm. of pyramidon, 0.02 gm. of ephedrin, 0.0002 gm. of lobeline, and 0.004 gm. of extract of belladonna. One or two tablets of theophedrin, taken at the beginning or during a bronchial asthma attack, check it. In cases of inflammatory processes in the lungs, particularly in cases of exacerbated chronic non-specific pneumonias, theophedrin does not produce the desired therapeutic effect.

Theophedrin is widely used as a preventive against bronchial asthma attacks, but if applied regularly, and particularly during the day-time, it has a bad effect on patients, causing sleepiness and heaviness in the head, loss of keenness of mind, forgetfulness, etc. Hence, theophedrin is contraindicated for precision and brain workers during the working day.

Antasman, imported into the Soviet Union from Czechoslovakia, is similar to theophedrin in both composition and effect.

Sulphuric acid atropine was used for treatment of bronchial asthma as early as the last century.

We applied sulphuric acid atropine in drops, in doses of 1-2 mg. two or three times a day, or for subcutaneous injections in doses of 0.5 to 2.0 mg. 1-3 times a day.

In some cases an extract of deadly dwale was administered in doses of 0.015-0.02 gm. two or three times a day.

In cases of pronounced vagotony an atropine course of treatment was applied, lasting from 3 to 4 weeks.

Most frequently, however, atropine was used episodically

in cases when ephedrin or injections of adrenaline proved to be of no avail. Available data, as well as our own observations, show that subcutaneous administration of 1 mg. of sulphuric acid atropine during an attack does not, however, produce in most cases any favourable result. Therefore, in cases of severe attacks of bronchial asthma or of a prolonged acute asthmatic state we most frequently injected intravenously sulphuric acid atropine together with adrenaline and pantopone when dealing with patients affected with complications; this removed the asthmatic state or checked the attack of bronchial asthma.

In addition, our patients received inhalation treatment—the smoke of leaves of the solanaceae family plants (deadly dwale, thornapple and henbane) mixed with potassium nitrate. This mixture, called "asthmatin" (2 parts of henbane, 8 parts of thornapple and 1 part of saltpetre), is manufactured by a galenic and pharmaceutical factory in Leningrad.

The application of asthmatin in patients not affected with any complications stopped the development of attacks when their premonitory signs appeared, and in some cases warded off the attacks themselves.

We recommended combined treatment with asthmatin and ephedrin in doses of 0.05 gm. which produced more pronounced results. The smoking of asthmatin proved less effective in patients affected with complications, but facilitated excretion of sputum and improved ventilation of the lungs.

Other mixtures of leaves of the same plants, manufactured both in the U.S.S.R. and abroad, were also used (Abyssinian powder, asthmatol, etc.). The smoke produced by burning the leaves of deadly dwale, thornapple and henbane, potassium nitrate and other drugs, when absorbed into the blood through the mucous membrane of the mouth and the respiratory tract, influences the central nervous system and its centres and has a subsequent effect on the parasympathetic innervation of the bronchi. Besides, both

the by-products, obtained in the process of burning, and the saltpetre stimulate the mucous membrane of the respiratory tracts and help the expectoration of secretion accumulated in the bronchi.

Thus, according to N. P. Kravkov, when sulphuric acid atropine is administered per os or injected subcutaneously, intravenously or through the respiratory tract, "atropine affects the central nervous system, the endings of the motor nerves of the smooth muscles, the secretory nerves of the glands and the endings of the vagus in the heart."

The introduction of 1 mg. of atropine removed the bronchial asthma attacks and the asthmatic state in 10 per cent of patients; in 90 per cent the attacks and asthmatic state continued. According to our own data and available publications the effect of sulphuric acid atropine is intensified when it is administered simultaneously with adrenaline or ephedrin.

Hence, we consider the administration of sulphuric acid atropine in therapeutic doses together with ephedrin or adrenaline as indicated during an attack or asthmatic state.

We also consider sulphuric acid atropine, irrespective of the way it is introduced, a good preventive against bronchial asthma attacks or an asthmatic state.

There are no contraindications for the use of atropine during attacks or an asthmatic state. Sulphuric acid atropine leads to an alteration in the state of excitation of the central nervous system, the cerebral cortex, the vital centres, particularly of the respiratory centre, and in the parasympathetic part of the vegetative nervous system; this, in turn, results in a change in the state of the dominant centres of heightened excitability. Bronchial asthma attacks are clinically checked.

We treated 28 bronchial asthma patients with chloral hydrate in doses of 0.5-2.0 gm. The chloral hydrate solution was administered at nightfall to prevent attacks at night, and in the day-time to check a prolonged attack.

There were no attacks at night during the action of chloral hydrate, but once stopped, they recurred with greater vigour.

The mechanism of action of chloral hydrate consists in that it lowers the excitability of the central nervous system and depresses the vascular centre, the heart and the respiratory centre. Under the influence of prolonged attacks patients with bronchial asthma may show a depression of the respiratory and vascular centres; the administration of chloral hydrate intensifies this phenomenon and may, as a result of the paralyzing effect on these centres, end in a collapse. Therefore care should be taken not to administer large doses of chloral hydrate to bronchial asthma patients during an attack.

We treated 5 bronchial asthma patients with insulin according to Vigierko-Zvansky's method. Insulin was injected subcutaneously during bronchial asthma attacks in doses of 40-50 units.

An hour or two later a hypoglycemic shock developed, following which the bronchial asthma attack stopped.

The attacks were checked for 8-10 hours and then again developed, without change. The patients were reluctant to take this kind of treatment which eventually was abandoned.

Twelve bronchial asthma patients were treated according to the method suggested by N. V. Belogolovy. The patients inhaled vapours obtained from a mixture of "carbol-menthol-camphor."

During the inhalation of vapours the attacks of bronchial asthma sometimes ceased, and then recurred a few minutes or hours later. The action of the vapours of this preparation is directed at the receptors of the respiratory tract mucosa, subsequently affecting the central nervous system and the dominant foci of heightened excitability.

The data published so far show that no generally agreed view exists as yet on the application of morphine to treat bronchial asthma patients during an attack. Some suggest the use of morphine and its preparations, others, on the

contrary, are dead against its use. In his text-book on pharmacology M. I. Gramenitsky writes: "In case of bronchial and cardiac asthma it is advisable to prescribe morphium alternately or in combination with papaverine."

N. F. Golubov suggests morphine through subcutaneous injections but cautions against injections in large doses, particularly at the end of an attack, when there is a large quantity of humid crepitation, since this may stop the evacuation of sputum and do no more than prolong the painful condition of the patient.

M. Y. Aryev is against the use of morphine because patients form a habit and abuse it although he admits that it is a most reliable means of checking an attack.

V. F. Zelenin asserts that when treating patients suffering from bronchial asthma and "having at his disposal adrenaline," he saw no reason whatsoever for using morphine.

In his *Principles of Pharmacology* N. P. Kravkov cautions physicians against administering morphine and its preparations to patients suffering from bronchial asthma during attacks, since "morphine weakens and paralyzes the activity of the brain, resulting in dulled pain sensitiveness and sleep followed by narcosis. . . . Morphine paralyzes not only the brain and the spinal cord, but the medulla as well, death setting in under phenomena of paralyzed respiration . . . the action of morphine on the respiratory centre may be considered as selective as on the pain centres."

From the above it may be assumed that after the administration of morphine the patients show, against the background of a depressed central nervous system, a depression of the respiratory and coughing centres, which leads to a lowered secretory function of the bronchi, a maximal stagnation of sputum in the bronchi, a lessened respiratory function of the lungs and to a number of other changes; the latter bring about embolism of the bronchi and bronchioles with subsequent atelectasis and inflammation.

In the case of three of our patients an injection of 0.01 gm.

of morphine during an attack led to paralysis of the respiratory centre, followed by death.

We observed time and again how an injection of morphine or its preparations would bring about a general improvement for three or four hours, only to be followed by a relapse: severe dyspnea and coughing appeared, sputum was not ejected, asphyxia became more intense, and adrenaline and ephedrin had no therapeutic effect. After a few hours many patients manifested a rise in temperature, exacerbated chronic bronchitis and the beginning of acute bronchopneumonia, or exacerbated chronic non-specific pneumonia. Hence, we believe that injections of morphine and its preparations are contraindicated for bronchial asthma patients, and caution physicians against its use.

First aid to patients affected with bronchial asthma, particularly to those who previously received morphine or pantopone, should be rendered with lobeline or its substitute cytitone. Lobeline is administered subcutaneously in doses of 0.01 gm. Should the condition of the patient prove grave, the same dose has to be injected slowly intravenously. The stimulating effect of lobeline on the respiratory centre lasts from 10 to 15 minutes; therefore, if no improvement follows, a repeated injection of the same dose should be administered. Lobeline has no cumulative effect.

The treatment of bronchial asthma attacks should be subdivided into treatment of light attacks and severe attacks accompanied by a prolonged asthmatic state. In treating light attacks, we successfully applied: a) ephedrin in doses of 0.25-0.05 gm.; b) aspirin in doses of 1.0 gm. with 0.1 gm. of pure caffeine; c) 0.5 gm. of pyramidon with pure caffeine; d) a combination of 1.0 gm. of aspirin, 0.1 gm. of pure caffeine and 0.05 gm. of ephedrin; e) smoking of cigarettes filled with deadly dwale, stramonium and thornapple leaves mixed with potassium nitrate; f) compresses on the back and chest; g) local foot and hand baths at temperatures ranging from 40 to 45°C.; h) massage of the back and thorax.

A good effect is obtained if patients make use of these preparations and the smoking of the mixture made of solanaceae leaves in the precursory period of the attack. The above preparations do not produce the desired effect when the attacks have taken a severe course. In such cases it becomes necessary to resort to subcutaneous injections of 1 mg. of adrenaline which most frequently has to be administered every 4 or 5 hours, until the attack ceases. Nor should we forget the use of intravenous injections of adrenaline and the possibility of administering it together with atropine. The same is true of lobeline and cytitone which have a good effect on bronchial asthma patients during a state of asphyxia.

Considerable difficulties are encountered when checking attacks with complications, accompanied by an excretion of large quantities of sputum. Such patients have to be given adrenaline in doses of 1 mg. every two or three hours, i.e., from 8 to 12 times a day. Internal and subcutaneous injections of ephedrin in doses of 0.025-0.05 gm. had little effect.

A. V. Vishnevsky's method of jugular vago-sympathetic blocks (unilateral or bilateral) and A. D. Speransky's skin blocks as well as other methods of novocaine treatment are also effective.

During severe or prolonged attacks, attended with cardiac or respiratory insufficiency, the indications are for a simultaneous injection of adrenaline with 1.0-2.0 ml. of a 20 per cent solution of caffeine sodio-benzoate or a 20 per cent solution of camphor oil in doses of 3.0-4.0 ml. three or four times a day. Oxygen is effective when asphyxia becomes more intense.

Symptomatic or pathogenic therapy should be prescribed individually, anti-bacterial therapy, for example, in the case of pneumonia, psychotherapy when severe emotions cause an attack, etc.

We consider morphine and its preparations as contraindicated during attacks and have therefore not applied them in practice.

CONCLUSION

In this paper on *Modern Methods of Treating Bronchial Asthma* we have given particular attention to the study of the part played by the central nervous system and the reflex arc: the lungs—the central nervous system—the lungs. According to the works of S. P. Botkin and I. P. Pavlov's work *The Inadequacy of Modern Physiological Analysis of the Effect of Drugs* pharmacology should seriously consider the action of various substances on the peripheral endings of the centripetal (afferent) nerves. "These endings should be visualized as being most varied and specific, like the endings of the nerves of the sense organs, each of them being adapted to its distinctive stimulant of a mechanical, physical or chemical nature," wrote Pavlov.

We believe that the impulses of bronchial asthma patients which flow from the periphery along the efferent centripetal paths into the central nervous system, when sufficiently vigorous and constant, create in the central nervous system —in the hemispheres of the cerebral cortex—excitation seats (according to I. P. Pavlov) or a pathological dominant of bronchial asthma (according to A. A. Ukhtomsky) in conformity with every law typical of the pathological dominant. It has always been our aim to interfere actively in the process of the bronchial asthma disease and influence it in a desirable direction.

We direct therapy at the body as a whole, considering all the processes occurring within it as being interrelated and interacting: the pathological processes are related to the physiological processes, and the body is connected with the biological and social environment.

Moreover, when applying treatment, we should take into account the hereditary properties of the body, the diseases the latter has been subjected to, the general reactivity of the body, etc.

We subdivide treatment of patients with bronchial asthma into: 1) treatment in the absence of attacks, i.e., during a

remission; such treatment is administered individually according to plan; 2) treatment during an attack, dealt with above.

Treatment in the absence of attacks has its specific features, therefore we single out three periods.

1. The specific infection allergy period, when the toxic infection (acute or chronic) is localized in the superior respiratory tract, bronchi and lungs. During this period aetiological therapy should be applied with a view in one way or another to remove from the body the site where its sensitization originates or has originated.

When localizing the site in the superior respiratory tract, surgical methods of treatment should be administered, chiefly operative intervention in the nasal cavity, nasopharynx, lungs, etc.

Besides surgical treatment, desensitization therapy should also be applied—treatment with sulfanilamide preparations, penicillin, streptomycin and other anti-bacterial preparations.

Particular attention should be devoted to preventive treatment of the respiratory organs in people hereditarily predisposed to bronchial asthma. Physicians in factories and polyclinics should make a special study of the morbidity of such persons, record such cases and keep them under observation.

2. The period of parallergy, when the conditioned reflex mechanism of the bronchial asthma attack has been thoroughly established. The normal reactivity of the body has been altered, and attacks set in through various stimulating agents which this time are no longer specific. During this period the toxic infection factor remains and is often one of the principal causes of the attacks. During this period aetiological and pathogenic therapy is recommended with the widest possible use of desensitizing therapy.

Aetiological therapy should aim at treating the toxic infection site, but one must bear in mind that its elimination

may not produce the anticipated result and the attacks of bronchial asthma may continue.

Of the pathogenic means, wide use should be made of protective therapy—treatment with novocaine, of desensitizing therapy, aero-ionization with a negative charge, aspirin, pyramidon, phenacetin, calcium chloride, treatment with embychine, caffeine and bromide according to I. P. Pavlov's method, and of psychotherapy.

The physical methods of treatment that can be recommended include roentgenotherapy, irradiation with ultraviolet rays, diathermy, ionophoresis of calcium, bromides, novocaine, adrenaline, ephedrin, and other methods.

From our viewpoint, only local health resorts, located near the patient's permanent residence, should be recommended for climatic treatment. If patients receive treatment at southern health resorts, their stay and treatment there should be prolonged, to six months or more.

3. The third period of complications is the most complex as far as the application of various therapeutic measures is concerned. During the period of complications we observe pronounced chronic vesicular emphysema of the lungs accompanied by cardiac and pulmonary insufficiency, psychoneurotic superpositions expressed in fear of an attack, etc. Aetiological or pathogenic therapy is advisable and should be applied in every case.

In the period of complications many factors bring about attacks of bronchial asthma which may set in without any apparent cause. During this period symptomatic therapy is indicated, directed against any definite syndrome interfering with the patient's normal life, such as combating pulmonary or cardiac insufficiency, etc. But planned measures of aetiological and pathogenic therapy should neither be forgotten. Experience shows, for example, that the elimination of the toxic infection site in this period sometimes leads to a considerable general improvement of the patient's condition, checking bronchial asthma attacks for a long time.

Of the other kinds of therapy, psychotherapy should be

applied in every case; this helps to establish contact with the patient, familiarize him with the plan of examination and treatment and bring home to him the fact that bronchial asthma is a disease attended with remissions. He should be made aware of the fact that periods of exacerbations may ensue under the influence of factors which formerly brought about attacks. Under no circumstances should the patient's mentality be traumatized during treatment. The patient's questions should be comprehensively answered, and all points of interest elucidated in the clearest way. Psychotherapy is the beginning and the end of the course of treatment, but contact with the patient should continue also in later periods.

The living and working conditions of the patient are factors of great importance. We think the physician should make it his business to go into such matters and, if need be, help the patient change these conditions. A case in point is helping the patient to receive an invalid allowance or change his profession; the physician should always notify the doctor of the enterprise where the patient is employed about the latter's needs in connection with his disease.

In some cases the physician has to certify that a change of residence is necessary: country life or a change of climatic conditions. As mentioned above, the indications are for a climate with insignificant precipitation and a constant mean annual temperature without drastic barometric fluctuations.

The above shows that bronchial asthma patients should be treated on the basis of individual plans of examination and treatment, with due account for their heredity, former diseases, environment, and the nature and conditions of work.

Complex therapy alone, assisted by rational psychotherapy, can produce favourable results and contribute to the recovery of the patients.

All these measures are successfully effected in the Soviet Union, where solicitude for the well-being and health of the people is the paramount task of the state.

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